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GLOBALIZATION OF MEDICAL AND CLINICAL RESEARCH:

ETHICS AND THE SEARCH FOR BENEFIT SHARING IN RESOURCE-LIMITED COUNTRIES

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General Introduction

The Globalization of Health Research in Resource-Limited Countries

Globalization is a well known concept that denotes the process of international integration, originating from the exchange of ideas, products and culture. It is a concept that involves economic integration, the transfer of policies and knowledge across borders, and the political relations and discourses of power among nations (Al-Rodhan & Stoudmann, 2006). In essence, globalization can be seen in many aspects of human interactions. Health research globalization entails the integration and cooperation between people in different countries in aspects that pertain to health research. Recent years have witnessed an increase in the globalization of health research whereby for-profit and not-for-profit oriented research is increasingly being conducted in countries other than where the research is originally sponsored (Glickman et al., 2009). The proportion of private for-profit sponsored research is almost equal to that of not-for-profit sponsored research. In 2006, the Global Forum for Health Research estimated that 48% of research is conducted by private for-profit organizations, 45% by public organizations and 5 % by private not-for-profit organizations (Global Forum for Health Research, 2006). Although, there is no specific estimate of the proportion of private for-profit research conducted in resource-limited countries, it is estimated that of the 50,000 international clinical trials conducted globally, more than 40% took place in countries with low health resources (Petryna, 2007). This increase in globalization of research in resource-limited countries has led to the coining of terms such as "research outsourcing", "north-south collaborative research", "exporting of research" and "research off-shoring". These terms are framed to depict the extent to which health research is increasingly being conducted in Low and Middle Income Countries.

Globalization of research can have positive impacts, transporting relevant research to address the health needs of countries that do not have the capacity to conduct their own research. For example, malaria vaccine trials are being conducted in many African countries and, when fully developed, the vaccine will have a major impact on the global control of endemic malaria (Schwartz, Brown, Genton, & Moorthy, 2012). Globalization of research is also vital in reshaping business models and ensuring greater economic growth of companies (Glickman et al., 2009). Nonetheless, critics of research globalization have classified the concept as exacerbating

the health disparities between developed and developing countries. These disparities are often the result of some partners exerting greater influence and reaping more advantages than other partners (in vulnerable conditions) within the globalizing research partnership. The health disparity between developed and developing countries is often symbolized by the popular metaphor of the 10/90 gap which describes how only 10% of the health research budget is targeted towards the health needs of developing countries which carry 90% of global burden of disease (Garrafa, Solbakk, Vidal, & Lorenzo, 2010). In addition, current trends in the globalization of research indicate that ease of participants recruitment, less stringent ethical oversight and low operational costs of research are the leading motivations for conducting "off-shoring" research to resource-limited countries (Petryna, 2007; Thiers, Sinskey, & Berndt, 2008).

Furthermore, globalization of research raises concerns regarding exploitation of research populations as well as other ethical challenges relating to clinical research in resource-limited countries (Glickman et al., 2009). Exploitation has been described by scholars from various theoretical standpoints (Ganguli Mitra, 2012). Wertheimer's account described on the last part of the thesis represents the most influential work on exploitation (Wertheimer, 1996). However, the term generally refers to something or someone being taken advantage of in order to further one's own interest (Macklin, 2003). In the context of health research involving human participants and communities, we are referring to the exploitation of people and their communities. Participants involved in research are entitled to a fair risk-benefit ratio and protection against harm during research and when this fair risk-benefit ratio and protection are not duly given, the research is said to be exploitative (Gbadegesin & Wendler, 2006). The situation of exploitation is particularly worrying if one considers research with the intention of commercialization whereby for-profit research sponsors stand to make surplus profit from the tangible research outcomes (e.g. a new medication) without providing or returning anything to the research participants and communities. It is morally wrong to exploit participants in a research and exploitation should to be guarded against whenever research organizations conduct research activities in resource-limited countries (Berg, 2001). One of the ways that controlling exploitation has been advocated in the research ethics literature is through the practice of benefit sharing. We turn now to describe the ethical concept of benefit sharing.

The Concept of Benefit Sharing

In this section, we present merely an overview of benefit sharing given that Part 1 of this work provides a full account of the concept, considering the different contexts and usage of the concept, as well as the justifications for benefit sharing in research. Although the concept of benefit sharing is often discussed in relation to international health research, it is not limited to this context, with discussions also arising in research involving the use of non-human genetic resources (De Jonge, 2010). In its broadest sense, benefit sharing seeks to address the issue of what research participants, communities and countries ought to receive as a result of their contribution or participation in research activities (Simm, 2007b). In other words, the concept concerns the provision of benefits, profits, advantages and incentives to the participants, communities and countries involved in research activities with the research sponsors. By research activities we are referring to all of the processes and resources involved in conducting both human and non-human genetic research. Within the framework of principles of biomedical ethics, the concept of benefit sharing can be linked to the principle of beneficence. This principle focuses on maximization of benefit and minimization of possible harms for participants in research (Mawere, 2012)

Having stated the meaning of benefit sharing, some ensuing questions arise regarding the concept: Is it necessary that individuals or communities participating in research always be given something in return for their participation? What benefits are appropriate for their contribution?

Participation in research activities has long been thought to be based on the idea of altruism such that human subjects are expected to participate in order to contribute to the improvement of the lives of others in the future (Jansen, 2009). Altruism is an ethical value centered on the premise that the moral worth of an individual is dependent on the individual's action and its impact on members of society, without any intention of self interest (Rushton, 1982). Therefore, altruistic motives pertain to actions embarked upon with the sole intention that the outcomes of such action would contribute in making other people in the society better. An example of altruism in medical research may be illustrated by participants of clinical trials who do so on a voluntary basis in order to help in the development of new therapeutic drugs for future patients without the presumption of any foreseeable benefit for themselves. These altruistic motives have good ethical appeal. However, there is now a greater realization that with the growing number of

globalized research projects, the altruistic motives of the research participants are not always reciprocated with altruistic actions on the part of the research sponsors (Simm, 2007a). Of particular interest are those research initiatives that aim at developing high profit commercial products. Petryna explains that the advent of "blockbuster drugs" (drugs with high commercial value) with sales of over a billion dollars annually has led to the increase in the clinical trials and commercialization of 'me-too' drugs, products that mimic the action of blockbuster drugs, with no significant improvement or alteration in their pharmacological properties (Petryna, 2007). Research sponsors also gain substantial profit from patent and intellectual property rights laws. These laws give sponsors exclusive rights to market a new product over a stipulated period of time. With these opportunities to developing drugs with high profit margins, it would be ethically dubious for research participants and communities to be invited to enroll in research on the basis of altruism.

Schroeder presents an example of this ethically suspicious practice within a research study involving the use of *jaborandi*—a plant found exclusively in the Amazon region of Brazil. The plant was obtained from the Amazon region by a German Pharmaceutical Company, Merck, and its medicinal properties (*alkaloids)* were refined and transformed into eye drops. Merck obtained a patent for the exclusive commercialization of the eye drops. The result of this commercialization is that any Brazilian wanting to use the product would have to buy them at German prices, and any Brazilian company wanting to produce a generic version of the treatment would be required to pay royalties to Merck for the period of the patent (Schroeder, 2009). In this case, it would be morally inappropriate for Merck to recruit individuals in a clinical trial of the eye drop and expect them to act in altruism while they subsequently gain profits from the marketing of the eye drop. This example represents an ethical tension that forms the basis of the normative ethical reflection that is addressed in Part three, chapter 1 of this thesis.

The issue of benefit sharing is not only applicable to pharmaceutical companies and for-profit research organizations. Academic research institutions as well as non-governmental organizations involved in research are expected to share the benefits of research with the host communities. Although these organizations are mostly not profit oriented, they can strive to ensure that their research has an additional social value.

Relevance of the Doctoral Research Project

As I have outlined, the drive for research that is motivated by the gains in profits has diminished the appeal of altruism and underscores the need to explore the ethics of benefit sharing. Nonetheless, the ethics of benefit sharing does not necessarily preempt the long term "tradition" of altruism in research. Rather, the concept is essential in providing an added value to the conduct of research.

As a bioethicist involved in research ethics, I consider it valuable to seek ways to balance the overall good of research between the research sponsors, research participants and communities. This search for the good of research is particularly important to the research participants and communities because they are relatively disadvantaged when compared to the research sponsors that exert more research influence. The search for good values of research in resource limited countries is not to put to a stop to the conduct of research in those countries, but to improve the ethical and social value of research. The processes involved in improving the social and ethical value of research encompass the concept of benefit sharing. In the same vein, within the broader principles of biomedical ethics, benefit sharing can be embedded in the principles of beneficence and justice (Beauchamp & Childress, 2009). Like the principle of beneficence, the goal of benefit sharing is to ensure the promotion of good and to provide positive benefits to research participants and communities. Likewise, benefit sharing is in line with the principle of justice because it seeks to ensure that research participants and communities are treated with utmost respect and are not exploited during research.

It is evident that the concept of benefit sharing is essential in health research, owing to its link with the principles of biomedical ethics. However, as important as this concept is, there is little empirical investigation on this concept within the domain of international health research in developing countries. I argue in this work that research ethics concepts, such as informed consent, have received more attention in research than benefit sharing. A look at the state of the art on the concept of benefit sharing reveals its importance in research ethics. Nonetheless, its nuances are not well discussed in the field. In most cases, benefit sharing arises when referring to the concept of exploitation and other concepts in research. Moreover, looking at the international guidelines for the conduct of research, benefit sharing is outlined as requirement. However, there are no clear consensus in different ethics guidelines on this requirement (Zong, 2008). As such,

the overall relevance of the work in this thesis is to provide more insight and an ethical voice to a concept that has not received adequate attention in research ethics.

Benefit sharing is well nuanced in research involving the use of non-human genetic resources. This could be attributed to the fact that non-human genetic resources were subjected to a lot of international treaties and discussions that culminated into a substantial framework of Nagoya Protocol (please refer to the first chapter of the first part of the thesis). In light of this, this doctoral research project is needed in order to develop more in-depth insights, discussions and ethical reflections that are relevant to making the concept of benefit sharing have a stronger advocacy than it has in international health research. These insights, discussion and reflections are essential in order to subsequently set the tone for the development of stronger and more robust frameworks that are specific to benefit sharing in international health research. Furthermore, this research project has added perspectives to the few empirical studies that exist within the field of benefit sharing in international health research (Kamuya et al., 2014; Lairumbi, Parker, Fitzpatrick, & English, 2012; Lairumbi, Parker, Fitzpatrick, & Mike, 2011; Molyneux, Mulupi, Mbaabu, & Marsh, 2012; Zvonareva et al., 2013). The research also has an added value in terms of the suggestion and recommendations we outlined in the last part of this work on the ways to achieve better benefit sharing outcomes.

Aims, Central Research Questions and Methodology of Doctoral Project

In general, benefit sharing refers to the act of giving something (such as a portion of profits, royalties, goods, advantages) to the participants, communities and the country that have participated in international health research or bioprospecting activities. This definition provides a broad spectrum that encompasses benefit sharing in both human and non-human genetic resources (Chapter 1). However, the main focus of this project is to investigate the concept of benefit sharing in the context of international health research in Low and Middle Income Countries. This was achieved through the following aims:

1. To conduct in-depth analysis of existing literature on benefit sharing in order to get an overview on the discourse on benefit sharing in international health research
2. To assess current perspectives and practices of benefit sharing among research stakeholders involve in international collaborative research Low and Middle Income Countries. These stakeholders include Ethics Review Committees in Nigeria, representatives of pharmaceutical companies, academic institutions and non-governmental organizations in Europe that are involved in the conduct of research in Low and Middle Income Countries.
3. To generate normative ethical insights and concepts and to provide recommendations on the practice of benefit sharing in international health research conducted in Low and Middle Income Countries.

Based on the aims above, we developed two central research questions for the doctoral project: 1) what are the perspectives and practices of benefit sharing among research stakeholders in Europe and Ethics Review Committees in developing countries involve in global health research in Low and Middle Income Countries? and 2) what are the normative ethical insights and concepts that strengthened benefit sharing in global health research in Low and Middle Income Countries?

The methodology adopted to answer these research questions was motivated by an ethical methodology that has been used in the past at the Centre for Biomedical Ethics and Law of the KU Leuven (Borry, Schotsmans, & Dierickx, 2004). The methodology employs a three-part investigation that consists of a general literature review, an empirical ethical inquiry and a normative ethical reflection which is achieved by a thorough and in-depth personal reflection on

the literature review and the empirical inquiry. Therefore, this doctoral research project begins with from a literature review of the various aspects of benefit sharing. The review provided the knowledge that was essential to proceed to an empirical ethical investigation in order to understand the current knowledge and practices of benefit sharing. Finally, the two parts have been brought into an ethical conversation in order to develop a narrative with the aim of developing new concepts or strengthening existing concepts on benefit sharing in international health research.

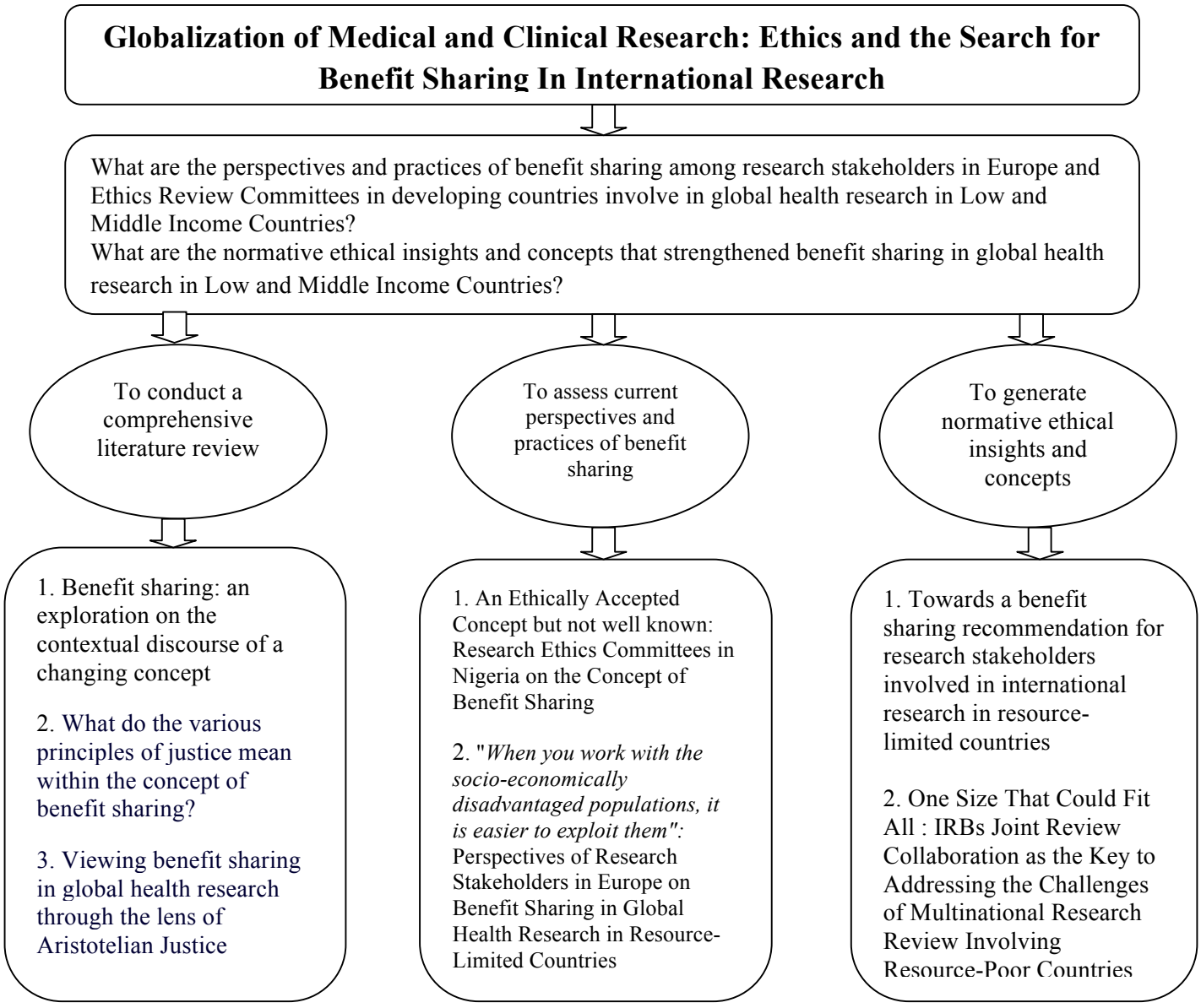

Figure 1: General Overview of the Doctoral Research Project

Part One: Literature Review on the Concept of Benefit Sharing

The literature review component is mainly concerned with getting a good understanding of the major nuances that have been documented in research publications regarding the concept of benefit sharing. This exploratory inquiry is essential in developing the empirical part and contributing to a good formulation of the ethical reflection part of the doctoral project. In looking at the concept of benefit sharing, it is essential to explore the origin and the usage of the concept in order to have a grasp of the complete picture of the concept. To embark on this exploration, the literature on benefit sharing was searched and collated. This literature was analyzed in order to understand the various contents and contexts on which benefit sharing was discussed. The use of a general literature review in the first part of the doctoral project was performed due to the advantages it offers (Boote & Beile, 2005). A general literature review is essential to assess the current state of a research topic and as a starting point in the doctoral project. We recognized this advantage as we examined the contextual discourses on the concept of benefit sharing. The general literature review is also crucial in identifying key issues that require further research. This advantage is paramount because the first review helped to generate further questions that we addressed in a systematic review and the empirical research part of the doctoral project. Furthermore, the general literature review was useful in identifying expert researchers and contributors on the topic of benefit sharing. Some of these expert researchers were suggested as reviewers for the manuscripts we submitted to international journals during the course of this doctoral project.

Conducting a systematic review was also valuable in the first part of the doctoral project. A systematic review is a specialized method used in research which involves an organized pooling of previous empirical research, appraising and synthesizing the results in order to answer a specific research question (Khan et al., 2003) . Systematic review methods have traditionally been used in medical research and it is regarded as a good method that provides high research evidence on a particular empirical research question (Khan et al., 2003). In recent times, a modified method of systematic review has been developed in the field of bioethics. This is known as systematic review of reasons (Strech & Sofaer, 2011). The main difference between this method and the traditional systematic review is its focus on assessing ethical reasons and arguments given for a particular phenomenon in bioethics (Strech & Sofaer, 2011). For example,

one can use a systematic review of reasons to assess the various reasons on whether euthanasia is ever morally permissible. The systematic review of reasons was employed to examine the various principles of justice provided as reasons for benefit sharing. Details of both the literature review and the systematic review of reasons are fully described in the first three chapters of this work.

Part Two: Empirical Research on the Concept of Benefit Sharing

In the second part of the doctoral project, the main nuances and arguments on the concept of benefit sharing are appraised and then tested through an empirical inquiry. The empirical inquiry is used to investigate the key ideas and arguments that were explored in the literature review. This part of the work represents an important aspect of this research project as only a few empirical research studies have been conducted on the concept of benefit sharing in global health research. Empirical research conducted with this thesis therefore provides a vital contribution to the body of knowledge on the topic of benefit sharing and the field of research ethics overall.

As this topic has few empirical research studies, qualitative research was favored as the best method of inquiry (Moriarty, 2011). Moreover, qualitative research was also favored because it focuses on testing documented and theoretical ideas in order to generate new meanings and themes related to a topic in question. This method is also useful to generate new theories. An example of this is grounded theory whereby inductive reasoning is employed to develop theories from the empirical data. This doctoral thesis focuses on testing documented or existing theories on benefit sharing. A quantitative method could also have been applied in the empirical studies. However, the choice of the qualitative method was based on fact that there are few existing empirical studies on the topic and therefore there is a need to establish new theories and strengthened existing ones through qualitative method (Green & Thorogood, 2014). The method of data collection for the qualitative research we employed was semi-structured interviews. This allowed a thorough interaction with the research respondents which promoted the generation of rich data (Dearnley, 2005). Semi-structured interviews pose open-ended questions which gives respondents the freedom to respond with adequate explanation. Question prompts are intermittently asked in order to ensure that responses are as exhaustive as possible (Leech, 2002).

The empirical research part of this doctoral project comprises two studies. These studies involved a total of 21 interviews with the selected respondents, each for approximately 1 hour. The first study was motivated by the need to investigate the nuances of benefit sharing among research stakeholders in a Low-Middle Income Country (LMIC). Nigeria was selected as an example of a LMIC. Nigeria was chosen due to the fact that the country is the most populous in the continent of Africa and is known for hosting many international collaborative health research studies. Over the past few years, Nigeria has developed relatively good ethical oversight for clinical research and trials in the country, sequel to the aftermath of the controversial Pfizer Trovan Trial. In this trial, children were administered an experimental drug (trovofloxacin), during a meningitis outbreak which resulted in the death of 11 children and several others were affected with brain damage and paralysis (Agunloye, Salami, & Lawan, 2014). In our opinion, it was essential for our topic to investigate what the perceptions of the ethics committee members in the country about the concept of benefit sharing in their experiences reviewing international collaborative research. Furthermore, the choice of Nigeria was motivated by the feasibility to conduct the study in the country. Having originated from Nigeria and worked as a Senior Pharmacist in the public health sector, I am very familiar with the research context and logistical difficulties. A total of 10 interviews were conducted in this study, however not all aspects of the interviews were analyzed and presented in this thesis. For this doctoral project, I only considered sections of the interviews that focused on benefit sharing.

The second study also utilized a qualitative method of analysis and semi-structured interviews for data collection. However, the study respondents comprised a range of stakeholders involved in research in Europe that are involved in the conduct of research in LMIC. The choice of stakeholders in Europe was motivated by the fact that no research on benefit sharing has been conducted with these stakeholders in Europe. The few empirical research studies that have focused on benefit sharing have solely targeted researchers, participants and other stakeholders situated in the LMIC. Conducting research among stakeholders that are situated in Europe who are significantly involved in research in LMICs offers a different perspective on the concept of benefit sharing. The stakeholders that participated in this research study were recruited from pharmaceutical companies, academic institutions and non-governmental organizations situated in

Europe. A total of 11 interviews were conducted in this study and, similar to the first study, not all aspects of the interview are presented here.

Part Three: Normative Ethical Reflection on Benefit Sharing

This part is highly relevant as it allows personal reflection and forethought on the literature review and empirical research part in order to develop novel ideas that are relevant to the concept of benefit sharing. Therefore, the aim of the normative ethical reflection is to bring together parts one and two of the doctoral project into an "ethical conversation" in order to arrive at an ethically based conclusion. This part consists of two sections that offer suggestive standpoints on the doctoral project. In the first section, we offer a recommendation on ways to improve benefit sharing in global health research in resource-limited countries. This recommendation is based on the new ideas and nuances that emerged during the literature reviews and empirical studies. This section also provides an evaluation of benefit sharing based on a spectrum of transactional exchange between two parties. The evaluation is essential as it provides a normative basis on which benefit sharing is justified.

In the second section, we assess an example of a benefit sharing activity in practice: capacity building of stakeholders in a resource-limited country. I argue in this section that North-South joint ethics review of research protocols is the most effective way of improving the quality of ethics reviews and to build the capacity of local ethics committees in developing countries. Capacity building is considered a type of benefit sharing whereby the local health staff involved in research activities are trained or educated in a skill, knowledge or technique to improve work output. This section is highly relevant to benefit sharing as it presents a good example of capacity building which fosters a better output of ethics review process among local ethics committees involved in international collaborative research. The section is originally built as a commentary from an original paper that discussed the various ways to improve ethics committees in a multi-centre trials (Barchi, Singleton, & Merz, 2014a).

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Part One: Literature Review on the Concept of Benefit Sharing

Part One Chapter One: Benefit Sharing: An Exploration on the Contextual Discourse of a Changing Concept

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Abstract

Background: The concept of benefit sharing has been a topical issue on the international stage for more than two decades, gaining prominence in international law, research ethics and political philosophy. In spite of this prominence, the concept of benefit sharing is not devoid of controversies related to its definition and justification. This article examines the discourses and justifications of benefit sharing concept.

Discussion: We examine the discourse on benefit sharing within three main spheres; namely: common heritage of humankind, access and use of genetic resources according to the Convention on Biological Diversity (CBD), and international clinical research. Benefit sharing has change from a concept that is enshrined in a legally binding regulation in the contexts of common heritage of humankind and CBD to a non-binding regulation in international clinical research. Nonetheless, there are more ethical justifications that accentuate benefit sharing in international clinical research than in the contexts of common heritage of humankind and the CBD.

Summary: There is a need to develop a legal framework in order to strengthen the advocacy and decisiveness of benefit sharing practice in international health research. Based on this legal framework, research sponsors would be required to provide a minimum set of possible benefits to participants and communities in research. Such legal framework on benefit sharing will encourage research collaboration with local communities; and dispel mistrust between research sponsors and host communities. However, more research is needed—drawing from other international legal frameworks, to understand how such a legal framework on benefit sharing can be successfully formulated in international health research

Keywords: Benefit sharing, Research ethics, International research, Common heritage of humankind, Biodiversity, Justice, Developing countries

Background

The concept of benefit sharing has been a topical issue on the international stage for more than two decades, gaining prominence in international law, research ethics and political philosophy [1]. This prominence of benefit sharing is mostly accompanied with controversies and contradictions associated with what the concept entails and what its definition is. Schroeder realizes this problem of definition, commenting, "for more than 15 years of entering into international law, benefit sharing has no entry in the Oxford English Dictionary and remains a technical word not used in everyday academic language"[2].

Nonetheless, navigating through the contexts where benefit sharing is prominent, we can find a definition that suits the concept as used in that context. For example, in the framework of the access and use of genetic resources, benefit sharing is described as "the action of giving a portion of advantages or profits derived from the use of genetic resources or traditional knowledge to resource providers in order to achieve justice in exchange" [1]. In the context of international research this definition is viewed differently; it is often viewed from the perspective of what participants and by extension the communities in developing countries ought to receive as compensation for their participation in research [3].

Differences in the discourses and justifications on benefit sharing form the basis for different definitions and also limit or broaden the concept. For example, a compensatory justice-based discourse may limit benefit sharing to the compensatory interaction which occurs between researchers and participants during research, while solidarity-based justifications broaden benefits to include all human beings [3]. It is these discourses and justifications that set the tone for this article. This article will provide an investigation into the changes in the discourses and justifications of benefit sharing in order to address the question of whether these changes affect the present practice of benefit sharing in international research. We examine these changes in three spheres. Firstly, we assess the discourse of benefit sharing in terms of the broader concept of the common heritage of humankind—we assess the emergence and the ethical disposition that benefit sharing concept is set to achieve in the common heritage of humankind. Secondly, we assess the concept in the context of the access and use of genetic resources as outlined in the Convention on Biological Diversity (CBD). Thirdly, we examine the concept as used in the

context of international clinical research with a focus on three formulations of benefit sharing. This article will familiarize the reader on the main discourses on benefit sharing. It is intended to contribute to awareness among stakeholders in health research on benefit sharing.

Discussion

We present an account of the three spheres on which benefit sharing is commonly discussed. Based on these spheres, we then map ethico-legal changes in benefit sharing and assess these changes as they affect benefit sharing in international research.

Benefit sharing within the context of the common heritage of humankind

The notion of benefit sharing first emerged on the international platform in relation to the concept of the common heritage of humankind [4]. The common heritage of humankind is a concept that deals with the fate of resources obtained from common heritage territories (the moon and other celestial bodies, as well as the sea and the subsoil beneath it). The concept of the common heritage of humankind evolved from the doctrine of *res communis* which delineates that resources obtained from common heritage territories are not meant to be monopolized, possessed or owned by individuals, communities or states; rather, the use of such resources has to be subjected to the rights and interests of all humankind [5,6].

The relationship between the common heritage of humankind and benefit sharing stems from one of the cardinal elements outlined in the common heritage of humankind framework, namely: equitable sharing of resources. This cardinal element is closely related to benefit sharing [4]; it calls for an equal distribution of resources and encourages global policies that foster a homogeneous state of affairs among all states with respect to common heritage resources. Developing countries have envisaged this benefit sharing as a tool that presents a solution to the disparities existing between developing and developed states [7]. Hence, it has been advocated that the benefit sharing of the common heritage of humankind should be extended beyond the sharing of tangible resources to other possible goods [7]. For example, some scholars point out that benefit sharing should also include the sharing of technology with other states. This is based

on the assumption that technology is a common heritage of humankind because it is an inheritance of our ancestors irrespective of their nationalities [8].

Notable international treaties that emphasize benefit sharing in their common heritage of humankind regimes include the United Nations Convention on Law of the Sea (UNCLOS) and the International Undertaking on Plant Genetic Resources (IUPGR). The UNCLOS stresses in article 140 paragraph 1 the need to share benefits to everyone irrespective of geographical location of states, whether coastal or land-locked. The Convention also indicates the need to particularly consider the vulnerability of developing states that may be at risk of exclusion from benefit distribution [9]. Also, plant genetic resources have been considered as part of the common heritage of humankind [4, 10]. This was indicated by the agreement of International Undertaking on Plant Genetic Resources (IUPGR). The agreement recognizes that plant genetic resources are a heritage of humankind to be preserved, and to be freely available for use, for the benefit of present and future generations [11].

The ethical appeal of equitable benefit sharing in the common heritage of humankind is targeted at achieving equality among all states with regards to resource distribution. The founder of the concept of common heritage of humankind, Arvid Pardo [12] clearly indicates this equality in a statement that: “the common heritage of humankind challenges the structural differences between rich and poor countries and revolutionizes international relations towards equality among countries” [13]. However, the reality of achieving equality of resource distribution remains problematic owing to the continuous power and economic asymmetry that exists among states. Mounting concern by developing countries about the uncompensated use of plant genetic diversity obtained from their territories pushed for a move against the common heritage of humankind concept and an adoption of sovereign rights to biodiversity [4]. It was argued that the common heritage of humankind and its benefit sharing requirements would encourage exploitation and biopiracy—a situation whereby bioprospectors travel to diversity rich countries and take resources without seeking permission or sharing benefits with host countries or local communities [14].

Benefit sharing in the context of the access and use of genetic resources according to the Convention on Biological Diversity (CBD)

The concept of benefit sharing has been concretized in the context of the access and use of genetic resources [15]. Genetic resources include both non-human genetic resources (e.g. plant, micro-organism and animal genetic resources) and human genetic resources (e.g. human DNA material, blood and other human tissues). In this context, benefit sharing denotes an exchange between those who grant access to genetic resources and those who provide benefits, rewards or compensations resulting from the use of the genetic resources [1, 14]. Unlike the common heritage of humankind concept, in the context of genetic resources, states hold a sovereign right over their natural resources and can grant access to those that require to utilize such resources under a condition of Prior Informed Consent (PIC) and Mutually Agreed Terms (MAT) of appropriate benefit sharing [16]. For example, a local community in the Amazon region of South America can negotiate a deal with plant scientists or bioprospectors to exchange plant material expected to have a medicinal property with medicinal products or royalties that subsequently result from the utilization of the plant material.

The concept of benefit sharing with regard to the use of genetic resources originates from the CBD. The CBD is said to mark the end of the era of the common heritage of humankind concept. In the CBD preambles, resources are deemed to be the "common concern" instead of the "common heritage" of humankind. It is the concern of all humankind to preserve and sustain the use of resources for humanity and future generations. However, the duty to preserve and sustain resources does not imply that resources are common heritage for all; rather, resources are the property of the states [10]. CBD declaration was first endorsed in 1992 however; the requirement of benefit sharing was fortified through a series of discussions by the Conference of Parties to the CBD which subsequently culminated into a more emphatic framework known as the Nagoya Protocol. The protocol which was adopted in 2010 provides a strong basis for greater legal certainty and transparency for both providers and users of genetic resources [17]. The legal certainties of the protocol require countries to develop laws to ensure that the use of genetic resources within their jurisdiction is done with prior informed consent and on mutually agreed terms, and that it complies with benefit sharing legislation in other countries. While the transparency aspect of the protocol require industrialized countries to set up one or more

checkpoints for disclosing what resources they have accessed and where, and to monitor whether they are complying with the protocol [17]. In general, the Nagoya Protocol addresses some critical gaps and uncertainties in the CBD regulations on benefit sharing and also sets in motion formal discussions on other unresolved topics and ideas [18].

The concept of benefit sharing here can be related to the ethical principle of justice in exchange or commutative justice. Justice in exchange demands that those who use resources give back due reward to the providers or custodians of the resources [19]. This type of justice has been quoted in articles to be related to Aristotelian notion of fairness in a transaction which holds that the intrinsic worth of something has to be matched by a proportionate requital either in kind or in pecuniary terms [4,19]. While the Access and Benefit Sharing (ABS) framework works for non-human genetic resources, human genetic resources could not be retained within the framework of the CBD. The Conference of Parties to CBD in 1995 excluded human genetic resources from the legal framework of its promulgation [20].

Benefit sharing and international clinical research

International clinical research refers to a research involving human subjects that is organized and sponsored by pharmaceutical industries, Contract Research Organizations (CROs) and other research organizations in industrialized countries but conducted or outsourced in resource poor countries [21]. International clinical research can be clinical trials of new drugs, testing of new diagnostic equipment or genetic research that involves the collection and storage of various genetic samples e.g. Genome Wide Association Studies. Outsourcing of research by pharmaceutical industries has been on the rise and is mainly due to the ease of patient recruitment, low overall cost of trial and relatively less stringent regulatory procedures in the outsourced countries. These reasons raise concerns on how to conduct research that is ethical in resource poor countries [21,22]. Benefit sharing is considered to be one of the important benchmarks for ethical research in developing countries [23]. Also, the discourse on benefit sharing in international research springs from the fact that large proportion of the populations in developing countries lives in poverty and cannot pay for their health care services. As such, health research conducted in these resource poor countries should uphold obligations of

providing the benefits of research in order to improve the healthcare services of these countries [24]

In human genetic research, the predominant stance on benefit sharing suggests a return to the concept of the common heritage of humankind. This is evident from the emphasis on an equal sharing of the benefits arising from human genetic resources to all of humanity. The conjecture in human genetic research is that human beings share 99.9 % of their genome; as such, human genes are considered to be resources of the common heritage of humankind, and all humans ought to share the collective duty to explore their genetic resources, preserve them and share equally the benefits derived from their utilization. This position was declared by the United Nations Educational, Scientific and Cultural Organization (UNESCO) Declaration on Human Genome and Human Rights (1997) and followed by the Human Genome Organization (HUGO) Committee on Ethics (2000). The main ethical disposition regarding benefit sharing in human genetic research is centered on solidarity, whereby everyone (not only the research participants) is entitled to the benefits derived from advances in genetic research. This is evident in the UNESCO declaration which states that "benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all" [25]. To demonstrate the need for commitment to support developing countries through benefit sharing, the HUGO ethics committee proposed that 1-3 % of the profits gained by research organizations should be set aside for charitable work in developing countries. Setting this figure was intended to provide a minimum requirement that would encourage companies to be good universal citizens [26].

Furthermore, benefit sharing in international research is viewed in three perspectives. Firstly, benefit sharing is viewed as the provision of post-research results of the proven intervention. In other words, when the intervention tested in research has shown to be effective, it should be made "reasonably available" to the host community. This so-called "reasonable availability" in research emerged during the debate on the standard of care to be accorded to research participants in developing countries [27]. Reasonable availability requires that research be tailored to the health needs of the host community and the research results be made available to the community at the end of the research [28, 29]. This requirement is found in international ethical guidelines for the conduct of research. For example, the Helsinki declaration states in

paragraph 33 that, “at the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits”[30]. It is noteworthy to know that a new draft of the Helsinki declaration is formulated and is geared towards a development of a new version of the Helsinki Declaration—the draft has a recommendation for amendments on the wordings of reasonable availability and benefit sharing”[31].

Reasonable availability can be seen in the light of justice as reciprocity. It is concerned with what people deserve as a function of what they have contributed to an enterprise or the society. In clinical research, justice as reciprocity means that something is owed to the research participants and the community even after their participation in a trial has ended, because it is only through their acceptance of risk and inconvenience that researchers are able to generate findings necessary to advance knowledge and develop new medical interventions [32].

Secondly, benefit sharing in international research is viewed through the lens of the fair benefit approach, whereby the research community and research sponsors enter into a bargain in order to derive what is appropriate and fair benefit(s) that the participants should accrue [33]. The fair benefit approach argues for proportionality of benefits with regard to the risks and burdens of participation in research. The higher the risk of participation in research, the higher the benefit accrued ought to be. The approach also delineates that fairness of benefit is concerned with how much benefit is given to the participants or community, not what type of benefit they accrue as in the case of reasonable availability [33]. The fundamental difference between the reasonable availability and fair benefit approaches is that while the former restricts benefits to the proven intervention only, the latter expands the range of benefits to other possible benefits besides the proven intervention. This difference is echoed by the Participants at the Conference on Ethical Aspects of Research: post-research intervention is one way to provide benefits to the community but not the only way, and it must not be considered a necessary ethical condition for research in developing countries [34].

Thirdly, benefit sharing can be viewed according to the maximin approach. Maximin places benefit sharing in a broader concept of global distributive justice and depart from the view that negotiating activities between parties (sponsors and participants or communities) should always favor the disadvantaged group in their benefit sharing formulations [35]. The maximin approach is suitable considering the marked power and economic asymmetry between research sponsors and the vulnerable research community. Such asymmetry makes the vulnerable population view research as an opportunity to access better healthcare or to improve their health conditions. As a result, research communities in developing countries that strive to access basic goods (e.g. healthcare) during research should be assured of some benefits in the spirit of global distributive justice for basic goods[27,36]. With regard to the fairness of benefit sharing, the maximin approach suggests that a threshold of benefits should be set, beyond which it would no longer be rational for a self-interested research sponsor to transact [35]. In more practical terms, maximin advocates that pharmaceutical industries that outsource research to poor communities provide the best deal of benefits so that the poor accrue more benefits from the excesses gained as a result of the research conducted in the poor community.

The main emphasis in the maximin approach is on benefits on a macro level—i.e. benefits that will improve the overall healthcare structures of the poor communities. This is in contrast to the fair benefit approach which relies on the procedural bargaining powers of the parties involved in the transaction [35]. The maximin approach is seen as a way in which general improvement in healthcare as a basic good can be obtained through research, and consequently the gap of health-related inequality between the rich and poor can be bridged. Furthermore, the maximin approach has a positive advantage in that it provides benefit to the community irrespective of whether a post-research product is developed or not from the research [37].

Ethical and legal changes on benefit sharing

From the foregoing discussion, it is clear that benefit sharing has undergone ethical and legal changes from its inception in the common heritage of humankind concept to its usage in international research (Table 1). Regarding the ethical changes, we can ascertain that the main ethical justification of benefit sharing changes in each context. In the context of the common heritage of humankind, benefit sharing is justified based on the principle of justice as equality

whereby everyone deserves the same dignity, respect and moral worth [38]. Justice as equality entitles every state as a matter of rights to the benefits derived from the common heritage of humankind and it would be unjust not to share equally the benefits arising from the utilization of these common heritage resources. This ethical disposition has changed in the premise of the CBD. The justification of benefit sharing in the CBD is fundamentally based on the principle of justice in exchange or commutative justice. This exchange is between states that provide genetic resources on the one hand and states that access/utilize such resources on the other hand. Justice in exchange demands that fairness is ensured in what is exchanged when states interact with each other [39]. Therefore it would be unjust for a state not to provide fair and equitable benefit for an exchange of plant or micro-organism genetic material given to her.

Table 1.Benefit Sharing Disposition in various contexts

Context of benefit sharing	**Main ethical justification**	**Parties involved in benefit sharing**	**Legal stance of benefit sharing regulations**
Common Heritage of Humankind	Justice as equality	All states of the universe	Binding regulations (e.g. UNCLOS 1982, IUPGR 1983)
Convention on Biological Diversity	Justice in exchange or Commutative justice	States the provide genetic resources States that utilize genetic resources	Binding regulations on states that ratified the CBD
International clinical research	Justice as reciprocity (reasonable availability) Procedural justice (fair benefit approach) Distributive justice (Maximin) Solidarity (Genetic research)	Pharmaceutical industries and research organization Research participants and communities	Non-binding regulations

In the context of international research, there are four major justifications that benefit sharing is based on. Firstly, taking on the discourse of human genetic research, benefit sharing is justified on solidarity reasons whereby participants, communities and other populations outside the research setting have the right to benefits from the fruits of the research. In other words, benefit sharing is a gesture of solidarity between research sponsors on the one hand and participants, communities and in extension other populations on the other hand. As participants contribute their genes for research in solidarity, sponsors should return back this solidarity by distributing benefits to participants and everyone [40]. Secondly, justice as reciprocity also provides a justification for benefit sharing in international research considering the "reasonable availability" viewpoint. Participants' contributions are reciprocated with products generated from research for their efforts, time and risks taken in research [33]. Thirdly, benefit sharing is also justified on the basis of procedural justice in international research. This is mainly seen in the fair benefit approach model [34]. Procedural justice is considered to be the main ethical disposition in the fair benefits approach because the approach emphasizes that fairness on benefit sharing is achieved when research participants and communities enter into a bargain or negotiation with the research sponsors in order to achieve fairness on benefit sharing—and the processes of negotiation or bargain must be made transparent to all. In other words as long as the negotiations between research sponsors and communities are transparent and the parties involved have reach an agreement, then the benefit sharing is said to be fair [34]. Fourthly, based on the maximin approach, benefit sharing is justified on the basis of global justice for health. In this case, background inequalities between research communities and research sponsors form the main reason for benefit sharing. On the basis of this health inequality, global justice demands that research benefits should not only target the small needs of the research community but also the large needs of basic healthcare of the community and strive for improved health systems [41]. In summary we can say that the main ethical justification of benefit sharing has changed from justice as equality in a concept of the common heritage of humankind to justice in exchange in the CBD and to four major justifications in the context of international research.

With regard to legal changes, benefit sharing has undergone a shift in terms of its force and protection under the law (Table 1). Under the common heritage of humankind concept, the concept of benefit sharing exerts protection as it is enshrined under a legally binding agreement.

States that endorse the common heritage of humankind law have to agree with its accompanied benefit sharing regulation. This also applies to the CBD regulation on the use of non-human genetic resources. The CBD is even more stringent as it has a separate binding agreement on benefit sharing (Nagoya Protocol) which legally regulates non human genetic resources. However, with regard to the use of human genetic resources and in international research the protection of benefit sharing by a binding document is absent. This represents a shift away from a concept that is protected by law to a non binding regulation as documented in the UNESCO Declaration on the Human Genome and Human Rights (1997), the HUGO Ethics Committee statement on benefit sharing (2000), the UNESCO Declaration on Bioethics and Human Rights (2005) and the Helsinki Declaration of the World Medical Association (WMA, 2008).

The question of importance hitherto is: do the changes in the ethical and legal stance on benefit sharing in international research affect the present practice of benefit sharing in international research? One can consistently hold the view that making a certain regulation into law gives it supremacy and makes it firm in terms of implementation among states [42]. In other words, regulations that are passed into law are meant to be taken seriously and states are obliged to abide to the regulations whether they suit their intentions or not. The law therefore is always devised to enforce a duty without consideration of individual choices. We can also assert that some laws are formulated from certain ethical features that are deemed fundamental to societal living and human co-existence. For example, the rich biodiversity in developing countries is important to human existence—the need to protect and sustain its utilization for future generation is of immense significance, hence the CBD law created to protect against uncontrolled use and biopiracy of the biodiversity [19]. It goes without saying that if benefit sharing in international research is to be taken seriously as a vital substance of global health research, then its regulations must be enshrined into a legally binding framework. The absence of a legally binding document to regulate benefit sharing in international research has undoubtedly affected the tenacity of its advocacy in practice.

Summary

Based on the account of the ethico-legal changes, we suggest that benefit sharing in international research be formulated into a legal framework, as this will underscore the need to take it more seriously. Benefit sharing should be formulated in such a way that the level of benefits accrued from research participation is correspondingly matched with certain parameters such as the type of research in question, the organization sponsoring the research, the purpose of the research etc. In other words, a map of different possible types of research should be made and this should be matched with minimum forms of possible benefits that correspond to the research in question. The research sponsors can provide more than this minimum form of possible benefits if they are willing, however the minimum standard of benefits are obligatory by law. For example, a sponsor collaborating in a malaria vaccine research with a community should provide a range of benefits—for instance, environmental fumigation services, distribution of insecticide-treated nets to members of the community, effective malaria treatments for participants that may develop malaria during research etc. This range of benefits would be considered to be the minimum standard that must be provided to the collaborating community. The collaborating research community can negotiate with the research sponsors for other forms of benefits they may prefer. All the procedures and agreements on research benefits between the sponsor and community must be properly documented and be legally binding. This legal framework is necessary because benefit sharing is mostly ignored even though it is regarded as an ethically sound concept in international research [43]. The legal framework will ensure that international research actors abide at all times to the set legal requirements of benefits whenever they interact with research communities. Furthermore, because benefits will be linked to legal promulgation, the local research community will be encouraged to collaborate and be more open in research because they are certain of benefiting from the fruits of research. A legal framework of benefit sharing will dispel the issue of mistrust between research sponsors and host states or communities where research is done. An example of such mistrust is seen in the recent case of the Indonesian government's refusal to provide H5N1 samples from its citizens to the international research community for vaccine development on the grounds that they are not sure if the benefits of such a vaccine would be shared fairly with the Indonesian people [44].

While we hold the view that a non-binding stance of benefit sharing affects its current standing in international research, we do not believe that the multiple ethical justifications in international research have also affected the stance of benefit sharing. The multiple justifications provide different ethical platforms on which the normative bearings of benefit sharing can be ascertained. As such, the multiple justifications only provide different pathways to benefit sharing formulations and do not weaken the normative ethical appeal of the concept, as Simms rightly puts: "the existence of various arguments [justifications] behind benefit sharing is not necessarily problematic in itself […] the justifications can however produce different benefit sharing rationale" [3].

We must affirm however, that while a legal framework of benefit sharing in international research would augment its practice, the ease of formulating such a framework is not a simple task. More research is needed in order to determine factors that will facilitate creating a benefit sharing law in international research. Research is needed to establish lessons from the enactment of CBD laws that will foster the development of a legal benefit sharing framework in international research. There is a need to critically ascertain other international legal frameworks that directly or indirectly affect the practice of benefit sharing e.g. the Intellectual Property Laws. Researches on different contexts, various stakeholders as well as the complexities of international research are needed to establish different forms of benefit sharing formulations that are feasible. Different benefit sharing formulations can be related to the type of research in question. This will help in establishing fairness of benefit with regard to the risk of research. Also, more justifications and motivations for benefit sharing among international research sponsors need to be investigated

Abbreviations

CBD, Convention on biological diversity; CROs, Contract research organizations; HUGO, Human genome organization; IUPGR, International undertaking on plant genetic resources; MAT, Mutually agreed terms; PIC, Prior informed consent; UNCLOS, United Nations convention on law of the sea; UNESCO, United Nations educational, scientific and cultural organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The article was developed at various stages of drafted manuscript. BD and KD contributed equally to the first draft. BD elaborated the various stages of the manuscript with thorough revision, editing and mentoring from KD during the pre-publication process. Both authors read and approved the final version of the manuscript.

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Part One Chapter Two: What do the various principles of justice mean within the concept of benefit sharing?

Based on:

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Abstract

Benefit sharing concept pertains to the act of giving something in return to the participants, communities and the country that have participated in global health research or bioprospecting activities. One of the key concerns of benefit sharing is the ethical justifications or reasons to support the practice of the concept in global health research and bioprospecting. This article evaluates one of such ethical justifications and its meaning to benefit sharing, namely: justice. We conducted a systematic review to map the various principles of justice that are linked to benefit sharing and analyzed their meaning to the concept of benefit sharing. Five principles of justice (commutative, distributive, global, procedural and compensatory) have been shown to be relevant in the nuances of benefit sharing in both global health research and bioprospecting. The review findings indicate that each of these principles of justice provides a different perspective for a different benefit sharing rationale. For example, commutative justice provides a benefit sharing rationale that is focused on fair exchange of benefits between research sponsors and communities. Distributive justice produces a benefit sharing rationale that is focused on improving the health needs of the vulnerable research communities. We have suggested that a good benefit sharing framework particularly in global health research would be more beneficial if it combines all the principles of justice in its formulation. Nonetheless, there is need for empirical studies to examine the various principles of justice and their nuances in benefit sharing among stakeholders in global health research.

Background

Benefit sharing raises concerns of justice because global health research and bioprospecting activities in resource-limited countries are sometimes characterized by unjust treatment of participants and communities in those region (Schuklenk & Kleinsmidt, 2006). Global health research here refers to health research involving human subjects that are sponsored by research organizations in developed countries but conducted in resource-limited countries. These global health research could be clinical trials organized by commercial research sponsors in developed countries but outsourced in resource-limited countries. Petryna (2007) outlined that some clinical trials are conducted in resource-limited countries for the following reasons: low cost of trial related expenditures, ease of participants' recruitment and less stringent regulatory oversights. Moreover, some of the clinical trials are conducted without fair benefits to the host communities (Petryna, 2007). Bioprospecting activities refer to the systematic exploration and research of new sources of chemical compounds, genes, micro-organisms, macro-organisms, and other valuable products from nature. Also, the term is use to depict the research on indigenous knowledge related to the utilization and management of biological resources (Castree, 2003).

In the past, there were cases whereby researchers obtained medicinal plants from resource-limited settings, develop them into profitable commercial products without arranging any benefit with the local settings where the plants were obtained (Schuklenk & Kleinsmidt, 2006). This concern of taking undue advantage of research participants and communities in global health research and bioprospecting is known as exploitation and needs to be minimized (Benatar, 2000).

One of the ways to minimize exploitation in research is through benefit sharing (Gbadegesin & Wendler, 2006). Benefit sharing pertains to the distribution of benefits but also, often implicitly, to the burdens arising from research and development activities. It concerns what is owed to those people who participate in research but also to those who might not have taken part personally but live in the same community or wider population where research is undertaken (Simm, 2007a). Historically, benefit sharing has evolved from a concept that is enshrined in an international legal framework of the Common Heritage of Humankind to a non binding ethical regulation in international research guidelines (Dauda & Dierickx, 2013). In the principle of the Common Heritage of Humankind, benefit sharing regulation is set to ensure that *all* states, irrespective of their international influence equally share the benefits derived from the resources

of the common heritage sites (the moon and other celestial bodies as well as the sea and sub-soil beneath) (Holmila, 2005). Similarly, benefit sharing within the regulation of the Convention on Biological Diversity (CBD) is enshrined as a law, making it an *obligatory* practice among countries that ratified the CBD regulation (CBD, 1992). The CBD regulation deals with the issue of research involving non-human genetic resources (such as plants, microorganisms and animals resources) and traditional knowledge obtained from bioprospecting activities. However, global *health* research involving human subjects and their genetic resources, the benefit sharing regulations are not written in binding documents but only indicated in non-binding international ethics guidelines for research conduct.

Justice is a complex concept that deals with fairness in benefits and burdens that persons deserve as a result of their particular circumstance and interaction with others in human interaction (Beauchamp & Childress, 2009). There are many aspects of human interaction whereby justice is prescribed (such as criminal justice, social justice, political justice, occupational justice, organizational justice, etc.). Each of these aspects of justice is ascribed to deal with a type of human interaction within the society. For example criminal justice deals with the human interaction that pertains to upholding laws, protecting citizens, prosecuting criminals who break the law, and institutionalizing guilty criminals (Bernard & Engel, 2001). Occupational justice deals with a different aspect of human interaction that focuses on promoting fairness, equity and empowerment to enable opportunities for participation in occupations (Durocher, Rappolt, & Gibson, 2013). This paper focuses on the principles of justice that are relevant in the distribution of benefits or burdens as a result of people's interactions in global health research or bioprospecting.

First of all, justice is linked to benefit sharing because it seeks to address fairness for the participants and communities in the distribution of benefits, advantages, profits and burdens in interaction with research sponsors such as the pharmaceutical companies and Contract Research Organizations (CROs) (Pratt & Loff, 2011). However, this link is not immediately clear since there are various principles of justice, according to which a certain situation of benefit sharing can be assessed as "just", each time in a different way. For example, the principle of distributive justice focuses on the fairness in the *distribution* of benefits and burdens with consideration of

the *inequality* among different persons or groups in the interaction. In other words, equals should be treated equally and unequals should be treated unequally in any given interaction. This is in contrast to commutative justice that focuses on the fairness in distribution based on contractual agreements with no consideration on the inequality of the different persons or groups in the interaction.

This article, examines the various ways in which justice is being understood when it comes to benefit sharing in global health research and bioprospecting activities. We explore the meaning of these principles of justice in benefit sharing, identify the reasons why these principles of justice are being applied to the concept of benefit sharing, and discuss the relevance as well as the drawbacks of each principle when applied to benefit sharing. The article departs from the method of the systematic review, presentation of results that highlights the principles of justice and discussions as well as evaluation of the various principles of justice as applied to benefit sharing.

Methods

The method used is a systematic review of reasons (Strech & Sofaer, 2011) and it consists of the following procedure: (1) Formulation of the research question and inclusion criteria; (2) Identification of publications that meet the inclusion criteria; and (3) Extraction and synthesis of data.

Review question and inclusion criteria

The central research question to the systematic review of reason is:

What are the various principles of justice and arguments used as reasons for benefit sharing in global health research and bioprospecting?

The inclusion criteria in a systematic review of reasons should be able to identify all the publications that include the reasons mentioned in the central research questions. It is also important to justify the inclusion criteria (Strech & Sofaer, 2011). Accordingly, we established the following inclusion criteria for publications in the review

i. We included peer reviewed articles, published academic literature, comments, book excerpts and reports that discuss the principles of justice that are conceptually related to the concept of benefit sharing. The inclusion of the different types of papers is to ensure a wide coverage of possible literature on the topic

ii. We only considered publications that discuss justice and benefit sharing within the context of global health research or bioprospecting activities because that is the focus of our research.

iii. We considered publications that were published between January 1980 and January, 2015. The choice of the year 1980 is based on the fact that the discourse on benefit sharing emerged in the 80's within the Common Heritage laws such as the United Nations Convention on Law of the Sea (UNCLOS). The discourses on benefit sharing became more pronounced after the Rio Convention on Biological Diversity in 1992 (Dauda and Dierickx). As such, the choice of 1980 provides a good time span that captures the needed publications for the review

iv. We only considered publications that were published in English language. This is because of the difficulty to have to translate all publications written in other languages into English.

Identification of all the literature that meets the inclusion criteria

Strech and Sofaer recommend that a database-specific search strategy should be used in identifying the literatures for a systematic review of reason. For example the use of Mesh terms in PUBMED should be employed to determine if the search keywords in the review are contained in the Mesh terms of PUBMED (Strech & Sofaer, 2011). In view of this recommendation, we conducted the search for publications using four electronic bibliographic databases: PUBMED, EMBASE, WEB OF SCIENCE (WOS) and GOOGLE SCHOLAR. The selection of these databases was motivated by their regular use in biomedical research. We used a database-specific search strategy in order to obtain an optimum output of the publications from each database.

For the PUBMED database, we first use the mesh term search strategy. The keywords “justice”, “benefit sharing”, “global health research”, “international clinical research” and “bioprospecting” were searched on the Mesh database. We noted that the keywords “justice” and “bioprospecting” were contained on the Mesh vocabulary. However, other keyword such as “benefit sharing” and “global health research” and “international clinical research” were no Mesh terms. Consequently, we did not include Mesh terms in our search. We built up our search strings using a combination four different combinations of search strings in order to obtain wide range of publications outcome. These included: “justice AND benefit sharing”, “justice AND international clinical research”, “justice AND bioprospecting” and “justice OR social justice AND benefit sharing OR post study benefit AND global health research OR international clinical research AND bioprospecting OR convention on biological diversity” We also use the same search strings for the other databases aside Web of Science that we used “benefit sharing AND international research AND convention on biological diversity”. For the Google Scholar database, we considered the search output of the first 200 publications for each search strings. We considered this number to be exhaustive as to retrieve relevant articles for the review. More so, the Google scholar setting was adjusted to order publications according to their relevance to the search topic (Table 1.)

It is important to note that at this stage of searching, not all publications obtained from the search result met all the inclusion criteria (Strech & Sofaer, 2011). To ensure that only the publications that present the research question were included in the review, we applied a method for selecting the publications that did meet the inclusion criteria. Firstly, we read the titles of the publications and excluded publications that did not in any way suggest any idea of the research question. For example, the publication “Comparative metabolic physiology in the 'omics' era: a call to arms, paws, flippers, and claws” does not suggest any idea in relation to the research question and has been removed from the publications. Secondly, we read the abstracts and full texts to select the publications that presented any principle of justice that serves as a reason for benefit sharing in the context of global health research and bioprospecting. Thirdly, after finalizing which publications were to be included for the review, a few more publications were added as a result of ‘snowball method’. The snowball method involves locating or tracking relevant articles within

the bibliography of the selected publications. The process of selecting the publications was independently conducted by BD and KD and the included articles were agreed by the authors.

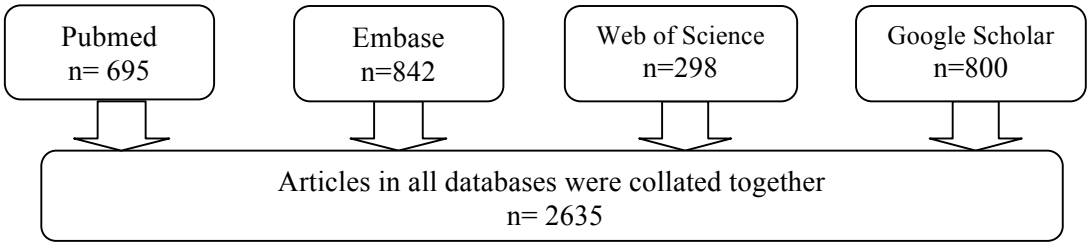
Table 1: Search strings used in the databases

Database	**Search strings**
Pubmed	"justice AND benefit sharing" "justice AND international clinical research" "justice AND bioprospecting" "justice OR social justice AND benefit sharing OR post study benefit AND global health research OR "international clinical research AND bioprospecting OR convention on biological diversity"
Embase	'justice'/exp OR justice AND benefit AND sharing AND [1980-2015]/py "justice AND international AND clinical AND research" "justice AND bioprospecting" "justice OR social AND justice AND benefit AND sharing OR post AND study AND benefit AND global AND health AND research OR international AND clinical AND research AND bioprospecting OR convention AND on AND biological AND diversity
Web of Science	"justice AND benefit sharing" "justice AND international clinical research" "justice AND bioprospecting" benefit sharing AND international research AND convention on biological diversity

Google Scholar	justice AND benefit sharing” “justice AND international clinical research” “justice AND bioprospecting” “justice OR social justice AND benefit sharing OR post study benefit AND global health research OR international clinical research AND bioprospecting OR convention on biological diversity”

Extraction and synthesis of data

Beginning at the level of abstract and proceeding to the level of full text, we read the content of the publications and grouped them according to the principle of justice given as a reason for benefit sharing. The publications assessment as to whether they present an analysis of principles of justice and benefit sharing was done independently among the authors. At the end the authors discussed and agreed on the publications that were included in the review. Publications were categorized into a particular principle of justice if they mentioned the principle of justice and analyze it with the concept of benefit sharing or fair benefits in global health research or bioprospecting. There were some overlaps as some of the publications presented two or more principles of justice and analyzed the principles with benefit sharing. As such, these publications were grouped in two or more sections. The sections that follow present our results and analysis of the findings.



Publications were stored in Refworks and duplicates (n=616) were excluded

n=2019

Publications were excluded (n=1819) based on titles and abstracts that do not convey any idea of the research question

n= 200

Articles were selected based on the reading of the abstracts and full text

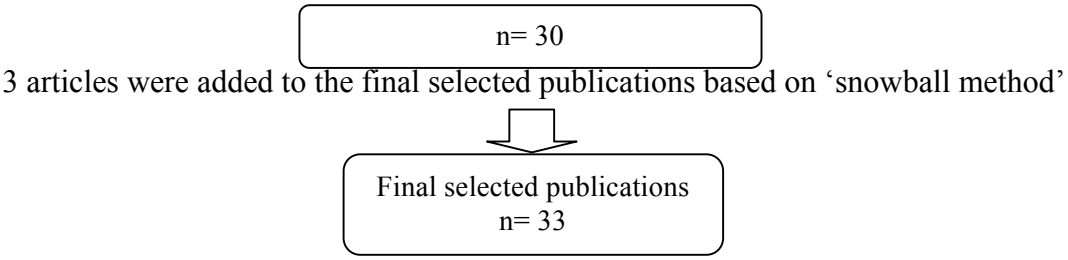


Figure 1: Database search of articles and selection process

Results

The initial search returned 2635 publications from the four databases. 616 duplicates were removed using the web based database, Refworks (Figure 1). After reading the title of the publications and some abstract, 1819 publications were further excluded leaving 200 publications. This is because their title or abstracts do not convey any idea or relevance whatsoever to the research topic. Reading of the abstract and full text of the publications narrowed the selected publications to 30 and the snowball method further added 3 publications. A total of 33 publications were finally included for the study. The publications included in the study are recorded in Table 2.

From these publications, we extracted five principles of justice that are linked to the benefit sharing concept in global health research or bioprospecting activities. These principles of justice are:

1. Commutative justice or justice in exchange
2. Distributive justice
3. Global justice
4. Procedural justice
5. Compensatory justice

We noted that commutative justice and distributive justice appeared to be the most predominant principles linked to benefit sharing in the reviewed publications. Distributive justice has been mentioned in more publications than commutative justice (Table 1); nonetheless, the two principles were mostly discussed in relation to each other. Global justice is the third most mentioned principle of justice along with procedural justice. While global justice is envisaged as a principle that broadens the course of distributive justice, procedural justice is noted to be relevant in ensuring fairness of procedures in both commutative and distributive justice.

Compensatory justice was noted to be the least mentioned principle. In the following paragraphs, we present detailed findings on each of the justice principles.

Table 2: Principles of justice analyzed within the concept of benefit sharing: Overview

Principle of Justice	Main ethical stance on benefit sharing	Limitation in application to benefit sharing	References of publications with the principle of justice
Commutative justice	Fair exchange of goods and resources	Limits application to only countries that own exchangeable resources	1. Bachmann, A. (2011). Ethical aspects of Access and Benefit-Sharing 2. De Jonge, B., & Korthals, M. (2006). Vicissitudes of Benefit Sharing of Crop Genetic Resources: Downstream and Upstream 3. De Jonge, B. (2010). What is Fair and Equitable Benefit-sharing? 4. Dauda, B & Dierickx, K. (2013). Benefit sharing: an exploration on the contextual discourse of a changing concept 5. Korthals, M., & De Jonge, B. (2009). Two different ethical notions of benefit sharing of genetic resources and their implications for global development. 6. Schroeder, D. (2007). Benefit sharing: it's Time for a Definition. 7. Schroeder, D. (2009). Justice and Benefit Sharing. In R. Wynberg (Ed.), Indigenous Peoples, Consent and Benefit Sharing:Lessons from the San-Hoodia Case 8. Schroeder, D., & Lasén-Díaz, C. (2006). Sharing the Benefits of Genetic Resources: from Biodiversity to Human Genetics. 9. Schroeder, D., & Pisupati, B. (2010). Ethics , Justice and the Convention on Biological Diversity 10. Schroeder, D., & Pogge, T. (2009). Justice and the Convention on Biological Diversity

Distributive justice	Distribution of benefits based on *need* of poor populations	Difficult to assign duties of benefits to only international research sponsors	1. Castle, D., & Gold, E. R. (2007). Traditional knowledge and benefit sharing: from compensation to transaction 2. Dauda, B & Dierickx, K. (2013). Benefit sharing: an exploration on the contextual discourse of a changing concept. 3. Vermeylen, S. (2007). Contextualizing "Fair" and "Equitable": The San's Reflections on the Hoodia Benefit-Sharing Agreement. 4. HUGO. (2000). Hugo Ethics Committee statement on benefit sharing April 9, 2000. 5. HUGO Ethics Committee. (2000). HUGO Urges Genetic Benefit-Sharing. 6. Hughes, R. C. (2012). Justifying Community Benefit Requirements in International Research 7. Pullman, D., & Latus, A. (2003). Clinical trials, genetic add-ons, and the question of benefit-sharing 8. Simm, K. (2005). Benefit-sharing: an inquiry regarding the meaning and limits of the concept in human genetic research. 9. De Jonge, B., & Korthals, M. (2006). Vicissitudes of Benefit Sharing of Crop Genetic Resources: Downstream and Upstream. 10. Schroeder, D., & Lasén-Díaz, C. (2006). Sharing the Benefits of Genetic Resources: from Biodiversity to Human Genetics. 11. Schroeder, D., & Pisupati, B. (2010). Ethics , Justice and the Convention on Biological Diversity 12. Schroeder, D., & Pogge, T. (2009). Justice and the Convention on Biological Diversity.

Global justice	Similar to distributive justice but more cosmopolitan perspective	-	1. London, A. J. (2005). Justice and the Human Development Approach to International Research. 2. Ballantyne, A. (2010). How to do research fairly in an Unjust World 3. Millum, J. (2010). How Should the Benefits of Bioprospecting Be Shared? 4. Pratt, B., & Loff, B. (2011). Justice in international clinical research 5. Pratt, B., & Loff, B. (2012). A framework to link International Clinical Research to the promotion of Justice in Global Health, 6. Resnik, D. B. (2004). The distribution of biomedical research resources and international justice. 7. Simm, K. (2007a). Benefit Sharing Frameworks-Justifications for and against benefit sharing in human genetic. 8. Simm, K. (2007b). Benefit Sharing: a Look at the History of an Ethics Concern 9. Chennells, R. (2010). Toward global justice through benefit-sharing.
Procedural justice	Ensures fair procedures of benefit sharing agreements	Achieving fairness in procedures between affluent and poor parties may be doubtful	1. Bachmann, A. (2011). Ethical aspects of Access and Benefit-Sharing (ABS). 2. De Jonge, B. (2010). What is Fair and Equitable Benefit-sharing? 3. Brody, B. (2010). Intellectual property, state sovereignty, and biotechnology 4. Ballantyne, A. (2008). 'Fair benefits' accounts of exploitation require a normative principle of fairness: response to Gbadegesin and Wendler, and

			Emanuel et al. 5. Participants. (2004). Moral Standards for Research in Developing Countries 6. London, A. J., & Zollman, J. . (2010). Research at the Auction Block. 7. Schroeder, D., & Pisupati, B. (2010). Ethics , Justice and the Convention on Biological Diversity 8. Coolsaet, B & Pitseys, J. (2015). Fair and Equitable Negotiations? African Influence and the International Access and Benefit-Sharing Regime 9. Vermeylen, S. (2007). Contextualizing "Fair" and "Equitable": The San's Reflections on the Hoodia Benefit-Sharing Agreement
Compensatory justice	Compensation for the inconveniences of research participants	May limit benefits to only direct research participants	1. Ndebele, P., Mfutso-Bengo, J., & Mduluza, T. (2008). Compensating clinical trial participants from limited resource settings in internationally sponsored clinical trials: a proposal. 2. HUGO Ethics Committee. (2000). HUGO Urges Genetic Benefit-Sharing. 3. HUGO. (2000). Hugo Ethics Committee statement on benefit sharing April 9, 2000. 4. Simm, K. (2005). Benefit-sharing: an inquiry regarding the meaning and limits of the concept in human genetic research. 5. Simm, K. (2007a). Benefit Sharing Frameworks-Justifications for and against benefit sharing in human genetic. 6. Simm, K. (2007b). Benefit Sharing: a Look at the History of an Ethics Concern.

Commutative justice

Commutative justice or justice in exchange refers to the principle of justice in relationships between individuals or groups, with specific respect to the *equitable* exchange of goods and fulfilment of contractual obligations (Sadurski, 1984)(Sadurski, 1984)(Sadurski, 1984). Commutative justice has been outlined as one of the fundamental reasons for benefit sharing. According to Schroeder, *"the justification for benefit sharing… relies on a mutually beneficial instrumental approach. In Aristotelian terms, one is dealing with 'commutative justice' or justice in exchange, where each party gives one thing and receives another, with a focus on the equivalence of this exchange"* (Schroeder & Lasén-Díaz, 2006)

The association between commutative justice and benefit sharing is mostly reflected within the broader discourse of the Convention on Biological Diversity (CBD). The CBD is an international legal treaty that aims at the conservation of biological diversity, sustainable use of its components and fair and equitable sharing of benefits arising from the utilization of resources. In principle, the CBD ascribes sovereign rights to the nation states over non-human genetic resources found within their national boundaries. Bioprospecting researchers wishing to use biological resources in states not within their sovereignty, have to abide with the requirement of benefit sharing. This requirement is justified by commutative justice, which emphasizes that communities in developing countries with the sovereign rights over their resources should be compensated in a fair way with other goods from the bioprospecting researchers. In other words, commutative justice places benefit sharing as an instrument for a *fair* exchange of goods with emphasis on *how much* a party receives in exchange with other goods (Bachmann, 2011; Dauda & Dierickx, 2013; De Jonge & Korthals, 2006; De Jonge, 2010; Korthals & De Jonge, 2009; Schroeder & Lasén-Díaz, 2006; Schroeder & Pisupati, 2010; Schroeder & Pogge, 2009; Schroeder, 2007, 2009)

The main problem of commutative justice as basic principle for benefit sharing, as outlined in some publications, is that it only has a *narrow* justification for benefit sharing. Authors have argued that commutative justice marginalizes poor states and communities that have no biological resources due to its narrow focus on *exchange* of resources with communities that possess biological resources. Only when you have resources, can you share in the benefits, when

you do not have anything you cannot (De Jonge & Korthals, 2006; Korthals & De Jonge, 2009; Schroeder & Pisupati, 2010). Consequently, authors have suggested that commutative justice should be combined with distributive justice (discussed in the next section) in justifying benefit sharing. The publications outlined that a combination of the two principles of justice would conceptualize benefit sharing not just as exchange that is based on possession of biological resources, but also as an exchange that is based on background disadvantages of poor communities (De Jonge & Korthals, 2006; Korthals & De Jonge, 2009; Schroeder & Pisupati, 2010; Schroeder & Pogge, 2009) Schroeder and Pogge maintain that *"CBD through commutative justice affords at best a partial remedy to the provision of basic needs … it is much more compelling to share benefits where it contributes to the fulfilment of basic needs and hence to the promotion of distributive justice* (Schroeder & Pogge, 2009).

Distributive justice

Distributive justice concerns matters of access to scarce resources among a group of people or a population. It deals with allotment of privileges, duties and goods in accordance with people's needs, contribution or responsibility; resources available to the society; and societal or organizational responsibilities with regard to the common good (Van Parijs, 2007). The principle of distributive justice implies that society has a duty to people in serious need and that all citizens have duties to others in serious need (Daniels, 2008a).

The reviewed publications show that the principle of distributive justice is well nuanced with benefit sharing in both bioprospecting research (Castle & Gold, 2007; De Jonge & Korthals, 2006; Schroeder & Lasén-Díaz, 2006; Schroeder & Pisupati, 2010; Schroeder & Pogge, 2009; Vermeylen, 2007) and global health research (Dauda & Dierickx, 2013; Hughes, 2014; HUGO Ethics Committee, 2000; HUGO, 2000; Pullman & Latus, 2003; Simm, 2005). The publications expressed that most developing countries have the problem of lack of the basic health care services and social infrastructures. Unlike the industrialized countries such problem is either absent or only exists on a minimum and fragmented scale. Based on these differences, the publications shared the view that global health research and bioprospecting research should strive at closing the global inequality gap through just distribution of research benefits to poor

countries (Hughes, 2014; HUGO Ethics Committee, 2000; HUGO, 2000; Schroeder & Pogge, 2009)

Praat (2011) expresses that there is confusion as to which research stakeholder should bear the responsibility of distributive justice as to perform benefit sharing in research. She noted that international guidelines mention different research stakeholders as responsible for benefit sharing. For example, while the *Declaration of Helsinki* mentioned *"physician"* as responsible for benefits, the UNESCO's 2005 *Universal Declaration on Bioethics and Human Rights (UDBHR)* mentioned *"nation states"*. Consequently, she noted that research sponsors are not solely obliged to perform duties of benefit sharing based on the principle of distributive justice (Pratt & Loff, 2011). However, in a counter observation, London (2005) noted that research sponsors have an obligation of human development in developing countries through global health research and benefit sharing (London, 2005). He argued for a human development approach in research which emphasizes on the need to place the obligations of research benefits on a broader justification of *global justice* and to take into consideration the responsibilities of other international research actors and organizations (London, 2005).

Global Justice

Global justice is philosophical concept that stems from a cosmopolitanism—a concept that envisages people as *global citizens* (Anthony, 2004). The notion of global justice presumes that just distribution of resources is not restricted to nation states and their national borders but extends beyond national boundaries to strangers and foreigners without preference for any one person over the other (Pogge, 2001)(Pogge, 2001)(Pogge, 2001)[36]. Accordingly, as globalization takes place in other aspects of human development, such as trade and economic globalization, health and healthcare research should also be part of this human development endeavour. As such, international health research should uphold global justice for health and provide research benefits in order to develop the healthcare system of the world's poor.

The reviewed publications denote/argue that global justice can be promoted through fair distribution of research benefits in resource poor settings. The publications accentuate global justice as a form of distributive justice that takes into consideration the inequality of social goods

such as healthcare that exist on a global scale (Ballantyne, 2010; Chennells, 2010; London, 2005; Millum, 2010; Pratt & Loff, 2011, 2014; Resnik, 2004; Simm, 2007a, 2007b). Millum noted that because the world is now a globalized community, the requirements of justice should not end only at the borders of nations but should be based on a broader concept of global justice beyond national borders (Millum, 2010). Other authors suggest that the most suitable way of promoting global justice through benefit sharing is by supporting sustainable access to proven medications as well as embarking on research projects that are responsive to the health priorities in host communities (Pratt & Loff, 2011, 2014; Resnik, 2004). Yet other publications further suggest that the provision of benefits should aim at improving the poor social infrastructures in developing countries. They noted that medical research should be linked to the contemporary discourse of social determinants of health—i.e. economic and social conditions that influence the health of people and communities. And based on global justice nuances, research sponsors should return benefits that would address these social determinants of health and improve the general social conditions and poor health in developing countries (Chennells, 2010; London, 2005).

Procedural justice

Procedural justice concerns the fairness and transparency of the processes by which decisions are made in a given transaction (Ambrose & Arnaud, 2005). In contrast to distributive justice, which concerns fairness in *outcome* of the distribution of goods and resources; procedural justice deals with the *process* or *procedures* that are involved in order to realize fair outcome in the distribution. As such, the basic idea is that whatever arises from a just procedure by just steps is in itself considered to be just.

Some of the reviewed publications outline the meaning of procedural justice in the nuances of benefit sharing process in both bioprospecting and global health research(Bachmann, 2011; Ballantyne, 2008b; Brody, 2010; Coolsaet & Pitseys, 2015; De Jonge, 2010; London & Zollman, 2010; Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2004; Schroeder & Pisupati, 2010; Vermeylen, 2007). The publications emphasize that procedural justice in bioprospecting research should be consistent with the requirements of a Prior Informed Consent (PIC) and a Mutually Agreed Term (MAT). In other words, only upon

the fulfilment of the two requirements of PIC and MAT in bioprospecting interactions, benefit sharing is considered to be fair and appropriate (Bachmann, 2011; Brody, 2010; Coolsaet & Pitseys, 2015; De Jonge, 2010; Schroeder & Pisupati, 2010; Vermeylen, 2007). Other reviewed publications emphasize the need of procedural justice in benefit sharing from the perspective of global health research. The emphasis stems from the fair benefit approach of benefit sharing. The fair benefit approach requires that host communities or their representative to negotiate with research sponsors for fair benefits in any given research interaction. For such negotiations to be fair, all processes of negotiations need to be transparent and parties ought to have equal bargaining power in the transaction (Ballantyne, 2008b; London & Zollman, 2010; Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2004).

However, some of the publications expressed concern on whether the procedural justice approach can actually ensure fair benefit sharing in the context of global health research. This concern stems from the power and economic asymmetry that characterizes the relationship between the research sponsors and the host research community. Authors have argued that research sponsors are likely to exert greater influence and bargaining power than the host communities who are mostly vulnerable (London & Zollman, 2010). Based on this imbalance in power and the vulnerability it is difficult to ascertain if the host communities are fully engaged or have the capacity to negotiate for fair benefits. Because of their vulnerable status, host communities might likely agree with *any* benefits even if the procedures in negotiating benefits are not truly fair (Ballantyne, 2008b, 2010; London & Zollman, 2010). For example, Vermeylen explains that in an interview conducted with the San community of Southern Africa, only a few knew about the benefit sharing agreements and others complained that their viewpoints on the agreements were not asked, let alone that they were actively involved in the negotiations process (Vermeylen, 2007).

Compensatory justice

The principle of compensatory justice refers to the extent to which people are fairly compensated for the disadvantages they are exposed to. It concerns paying back for the losses suffered and aims at restoring some status quo of the disadvantaged group. In order to be just, compensations are required to be proportional to the losses inflicted on a party (Hill, 2002).

The meaning of compensatory justice principle in the nuances of benefit sharing stems from the fact that participants have contributed time and effort in addition to risk exposure in research and should therefore be compensated fairly (HUGO Ethics Committee, 2000; HUGO, 2000; Ndebele, Mfutso-Bengo, & Mduluza, 2008; Simm, 2005, 2007a, 2007b). Simm summarizes compensatory efforts in benefit sharing as follows: "*the risks posed to participants in clinical trials can be serious and direct, as new medical interventions are tried out and evaluated. Benefit sharing within this context would be a compensatory activity geared towards those who have taken risks and accepted the possible inconveniences that are necessary if research is to take place and possibly succeed"* (Simm, 2007a).

The review publications outlined a limitation of the principle of compensatory justice as applied to benefit sharing. The principle narrows benefit sharing obligations only to the *direct* research participants and not to the entire communities. This is because, in accordance with the principle of compensatory justice, only direct research participants experience risks and injuries related to research, and thus deserve compensation (HUGO Ethics Committee, 2000; Simm, 2005, 2007a). However, Hughes (2012) counteracts this argument by stating that research often places burdens not just on individuals but also on the host community *as a whole*, most often by placing burdens on the community's *public* resources. For example, research sponsors may use the clinic of a community; the staff of the clinic may be involved in the research, thereby reducing the time they are supposed to spend on direct medical care to patients in general. As such, Hughes asserts further that if research sponsors place burdens on a community with limited means, they should provide some form of benefits to the community, such as providing hospital equipments, providing potable drinking water, building of community town halls etc. These may serve as fair compensations to the host community (Hughes, 2014).

Discussion

This is the first review that systematically analyses what justice in benefit sharing actually means, when taking the relevant publications on the theme in close review. The analysis provided in our results indicates that the principles of justice provide good justifications for

benefit sharing in both global health research and bioprospecting activities. However, each principle of justice in this review provides a peculiar justification for a different benefit sharing rationale. In other words, each principle has situated benefit sharing in a different form of distribution of health research goods and resources. For example, the principle of commutative justice supports a benefit sharing rationale with a focus on equal exchange of resources between the parties involved in a research activity. Benefit sharing is, as such, envisaged as a *tool* for exchange of goods and resources between research sponsors and host communities (Dauda & Dierickx, 2013). An important emphasis on the principle of commutative justice is that of the fairness of what is to be exchanged in any given transaction and not the background conditions of individuals or groups involved in a transaction. The parties involved are envisaged to possess equal rights in the transaction and are able to negotiate for goods without any external influence. Denier (2007) rightly put this notion that *all actors in the exchange should be considered as free and equal economic subjects whose personal differences in class should not play a role [in a negotiation] on the market* (Denier, 2007).

The implication of this principle of commutative justice, as it applies to research benefit sharing, is that global health research can be reduced to a market-like transaction. In principle, researched communities can enter into a bargain with the research sponsor on what benefits to exchange in a research. In reality, however, researched communities do not have good bargaining power. Because they enter a research project in order to access basic healthcare goods, they would often be willing to accept research benefits that may not actually be fair benefits (Ballantyne, 2010). As such, the research sponsors could – in principle take advantage of the research bargain. London further explained this complex relationship that *"in situations of enormous inequality of bargaining power, as is the case between impoverished research populations and for-profit research sponsors, open bargaining about the distribution of benefits is unlikely to result in the research population receiving more than a minimal share of the surplus benefit"* (London & Zollman, 2010). Consequently, commutative justice as applied to benefit sharing could turn research activities into what London calls an *auction block* whereby research sponsors could selectively conduct research in communities with minimal benefits demands in order to maximize their profits (London & Zollman, 2010) . As such, the review findings suggest that the

principle of commutative justice in itself is not enough as a justification for benefit sharing in global health research.

Our results indicate that authors are in favour of combining commutative justice with distributive justice principle in justifying benefit sharing (De Jonge & Korthals, 2006; Korthals & De Jonge, 2009; Schroeder & Pisupati, 2010). This is because distributive justice takes into account the background conditions of individuals or groups involved in a transaction (Denier, 2007). This implies that the benefit sharing rationale from a distributive justice perspective would consider the inequalities, the differences in power and research influence between researched communities and research sponsors in its benefit sharing formulation. Benefit sharing understood within the light of the principle of distributive justice is therefore, a cooperative interaction whereby the impoverished researched communities are given benefits due to their background disadvantages (Ballantyne 2010). We uphold the review results that distributive justice should be combined with commutative justice because they both complement each other in justifying benefit sharing. While commutative justice ensures that the researched communities receive the benefits they deserve in a fair exchange, distributive justice would consider the health needs and poor backgrounds of the researched communities in benefits distribution.

Furthermore, our review showed that distributive justice and global justice are similar because they both aim at distributing benefits with consideration to the least advantaged group. However, their major difference is in the scope of their application. While global justice has a wider scope of benefit distribution beyond the boundaries of a nation state, distributive justice focuses mainly on distribution of benefits among citizens within a nation state. The global justice principle is thought to be important in a globalized world where there is increasing global interaction and cooperation between nation states with different political and economic structures (Miller, 2008). The similarity between distributive justice and global justice is reflected in Rawls' seminal works. In *A theory of Justice,* Rawls establishes that distributive justice comes into play only within the context of society's basic structures. And only persons with shared basic structures have claims upon and responsibility to each other arising from considerations of distributive justice (Rawls, 1999a). However, in *The Law of Peoples*, Rawls incorporates a more global

(international) justice approach to distribution of goods. He proposes a duty to assist other people living in unfavourable conditions that prevent their having a just or decent political and social regime (Rawls, 1999b).

With regard to the procedural justice principle, our review indicates that the principle supports other principles of justice in benefit sharing (Bachmann, 2011). This is because the principle is concerned with how decisions are being made in any exchange or distribution of resources. For example, if a benefit sharing rationale follows a commutative justice principle, then procedural justice strengthens this benefit sharing rationale by ensuring that the processes involved in applying the commutative justice principle are strictly adhered to, and made transparent. Some theories of procedural justice suggest that fair procedures and good interaction among parties involved in a transaction can lead to equitable outcomes even if the requirements of other justice principles are not met (Bone, 2003). For example, it has been shown that good inter-personal interactions and transparency often associated with procedural justice has stronger tendency in affecting the perception of fairness in conflict resolution (Bone, 2003). While we agree that this can be true for conflict resolution, we cannot ascertain that the notion of good inter-personal relationships in itself is enough to produce just benefit sharing *outcome* in a research interaction. A close notion to interpersonal relationships in global health research is *community engagement*. Community engagement is the process of working collaboratively with local partners in order to build active participation and mutual respect (Tindana et al., 2007). It has been noted that community engagement is relevant in research in resource-limited countries (Tindana et al., 2007). However, further research is required to determine if community engagement alone can ensure fair benefit sharing outcome in a global health research.

Finally, our results suggest that the principle of compensatory justice justifies benefit sharing in global health research and bioprospecting. The results outline that compensations are obligatory in research due to the time spent in research participation, risks associated with trial medications, efforts spent and inconveniences that the participants and communities have incurred in research (Ndebele et al., 2008; Simm, 2005, 2007a). However, it is rather unclear whether compensations for inconveniences should be seen as a form of benefit sharing (Kamuya et al., 2014). No reason

is given for this obscurity. However—in our opinion, compensation in research is an obligation of the research sponsors irrespective of whether the research generates profits for them or not. For example, it is expected for research sponsors to provide transportation fare for participants that would have to travel to research clinic for appointments. It is also expected for the researcher to provide ancillary care for any unintended effect arising from the research. Benefit sharing on the other hand, can be argued to be applicable in research only when the research sponsors are set to realize profits. Furthermore, the fundamental outlook of the compensatory justice principle is focused on paying back for losses suffered by a victim that is inflicted by a victimizer (Hill, 2002). This has a strong negative or criminal connotation, which in our opinion should not be equated to health research activities. Global health research is not an activity whereby research sponsors are set to inflict pain to the researched participants and communities—it is rather, a research activity that places a priority on improving health and achieving equity in health for all people worldwide but especially in disadvantaged populations.

Conclusion

From this reason-based review, we can conclude that the principles of justice provide essential and fundamental arguments in favour of benefit sharing in global health research and bioprospecting. Various principles have been shown to support the benefit sharing concept. However, while we maintain that each of these principles is relevant in benefit, we suggest that a combination of all the principles provides a stronger reason for benefit sharing. Simm maintains a similar stance by indicating that combining multiple justifications for benefit sharing produces different perspectives for a benefit sharing rationale (Simm, 2007b). Accordingly, we recommend a benefit sharing framework that would encompass all the principles of justice in support of benefit sharing. For example, the Nagoya protocol on Access and Benefit Sharing has a benefit sharing rationale that is based on both the commutative and procedural principles of justice (Bachmann, 2011). Based on this review, we are convinced that such a framework could be even more beneficial if it also encompasses the other principles of justice, such as distributive justice and global justice. Furthermore, we suggest empirical research to determine the standpoints of stakeholders involved in global health research and bioprospecting activities on

the various justice reasons given for benefit sharing. This would be highly essential in the formulation of a good benefit sharing framework in global health research.

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Part One Chapter Three: Viewing Benefit Sharing Through the Lens of Aristotelian Justice

Based on:

Dauda B and Dierickx K. Viewing Benefit Sharing Through the Lens of Aristotelian Justice. *Journal of Medical Ethics. Under Peer Review*

Abstract

The ethics of benefit sharing has been a topical issue in global health research in resource limited countries. It pertains to the distribution of goods, benefits, advantages to the research participants and communities for their participation in research. One of the nuances of benefit sharing is on the ethical justifications on which the concept should be rooted on. Many literatures have outlined different principles of justice as justification for benefit sharing. This paper looks at these benefit sharing justifications from an Aristotelian justice approach. The paper assesses the central idea of Aristotelian justice, applies and evaluates this idea to the concept of benefit sharing with specific focus on commercial research sponsors that conduct research in resource-limited countries. The paper analyses Aristotelian universal justice and particular justice. Within the nuances of universal justice, the paper delineates that benefit sharing would mean obeying the set rules, regulations and legal framework on benefit sharing. However in the absence of legal frameworks on benefit sharing in global health research, we need ethical justifications for benefit sharing. Accordingly, the paper presents three perspectives of particular justice that provide the ethical justification for benefit sharing in global health research. As Aristotelian justice is still relevant to the contemporary discourse on justice, this paper has broadened the ethical justifications of benefit sharing within the justice framework in global health research.

Introduction

Participation in global health research has been known to have altruistic stance whereby research participation is viewed as individuals' contribution to the advancement of medicine and for the benefit of other patients (Berg, 2001; Hunter, Corcoran, & Leeder, 2012). While this altruistic notion is still important in medical research, there is a growing emphasis on the need for research participants and communities to accrue some benefits for participating in research. The emphasis on accruing benefits to research participants is even more echoed considering the proliferation of for-profit research sponsors that outsource research in developing countries (Simm, 2007a). Studies have shown that participants were motivated by the benefits they perceived in a research, particularly the information and care received during the medical examinations than an appeal to altruism (Mein et al., 2012). The ethics of giving a portion of benefits to research participants and by extension the research communities is contained within the concept of benefit sharing. It is a concept that deals with the fair allocation of advantages, profits and fruits of research by the research sponsors to the host research participants and communities. There is a widespread agreement that individuals and communities that participate in a research ought to have some benefits from the research, especially when such research is on commercial products that generate profits to the sponsors and the research is conducted in resource-limited countries where there are many health care challenges (Ballantyne, 2010).

Furthermore, assuming that for-profit research sponsors would gain surplus profit from a proven medication after a trial in a resource-limited country—then it would be ethically right to allocate *fair* benefits to the research participants and communities that have contributed in the trial (Knoppers, 2000). However, if such fair benefits are not allocated, we would presuppose a case of exploitation—a circumstance whereby the research sponsor is said to have taken undue advantage of the research participants and communities (Knoppers, 2000). Exploitation raises a concern of justice and justice seeks to restore *fairness* on what the participants and their communities ought to accrue due to their contribution in a research activity (Benatar, 2001). There are different perspectives of justice and each of these perspectives presents different rationale as to what fair benefits in research interaction ought to be. For example, a commutative

justice perspective views benefit sharing as an instrument of exchange. In this perspective, a benefit allocation in a given research interaction is considered *fair* only when there is an equivalent exchange of benefit between the research sponsors and the researched community (Schroeder & Pisupati, 2010). The commutative justice perspective does not consider the inequality between the research sponsors and the researched communities—rather, it only considers whether the resources to be exchanged between the sponsors and host communities can fairly be equated. In contrast to the commutative justice, the distributive justice perspective considers the inequality of the research sponsors and researched communities in its benefit sharing rationale (De Jonge, 2010; Schroeder & Pisupati, 2010).

This paper elaborates on different justice perspectives as they relate to benefit sharing from a philosophical underpinning of Aristotelian concept of justice. Current literature on the discourse on benefit sharing associates benefit with only Aristotle's notion of commutative justice (De Jonge & Korthals, 2006; Schroeder, 2007). This paper takes a further step by assessing the central idea of Aristotelian justice, applying as well as evaluating it to the concept of benefit sharing. The paper departs from a comprehensive overview of the Aristotelian concept of justice and then provides an analysis of the concept as it applies to benefit sharing.

Aristotelian Concept of Justice

In his seminal work of the *Nichomechean Ethics*, Aristotle distinguishes between two types of justice: *universal* justice and *particular* justice (Aristotle, 2000, 2011). The universal justice otherwise known as the general justice is related to the moral uprightness of a person to lawful conduct. Lawful conduct would demand that a person acts in accordance to the law and not to act in ways that would injure others in the society. Lawful conduct, according to Aristotle can encourage the development of *virtues* in a person. For example, the law can encourage or even force a soldier to remain in the war front and thus igniting the virtue of courage (Rosen, 1975). As such a person acting in accordance to universal justice would develop other virtues by simply abiding to the prescribed laws. Justice in a universal sense is therefore a *special virtue* because it encompasses all other virtues and it involves one's relationship with others. A just person is one that acts according to the law in an honest, modest, courageous, moderate and wise way. It goes

without saying, according to Aristotle, that to be dishonest or to act cowardly is to act unjustly (Aristotle, 2000).

Aristotle recognizes that the practice of lawful conduct as dictated by justice in the universal sense would not necessarily lead to the fullest development of virtues in a just man. In other words obeying a prescribed law in a given society does not entirely define a person as a just person in a society as regimes vary considerably from one another (Williams, 1980). For example, what might be considered lawful or virtuous conduct in an oligarchy regime might be regarded as unlawful and a vice in a democracy. Aristotle recognizes this tenet and proposes justice in the particular sense. He describes particular justice as that which concerns to the fairness and equality on which things have to be shared to deserving members of the society(Pakaluk, 2005). Particular justice takes note of those acts that might be unjust and are not recounted in the prescriptions of the law. In other words justice in *particular* sense transcends beyond individuals compliance and non compliance to the prescribed law to a domain where everyone is rendered a just proportion of property (Denier, 2007). Aristotle grouped particular justice into three categories based on: the criterion of distribution of goods (distributive justice), correction of private transactions that have gone wrong (corrective justice) and the reciprocity in exchange of goods and services (commutative justice). These various particular types of justice are considerably relevant in the current discourse on justice which in turn is relevant to benefit sharing.

Aristotelian Concept of Justice and Benefit Sharing

Hitherto, we have noted that benefit sharing is essential in global health research especially when for-profit research sponsors conduct research in resource-limited countries. We have also assessed the Aristotelian concept of justice based on universal and particular justice. In accordance to universal justice, for-profit research sponsors are expected to act justly by obeying the set laws and regulations on benefit sharing. For example, commercial biotechnological companies that would want to obtain a non-human genetic resource for a research would have to act in accordance with the Nagoya Protocol on Access and Benefit Sharing (Nagoya Protocol, 2010). This is because the Nagoya Protocol represents an important binding regulation on benefit

sharing. As such, for-profit research organizations within the non-human genetic research that act in accordance to the lawful provisions of the Nagoya Protocol would be acting justly and in line with Aristotle's universal justice. In the same vein, pharmaceutical companies that conduct global health research would act justly and in accordance to universal justice if they would abide by the benefit sharing provisions given in international ethics guidelines such as the Declaration of Helsinki, CIOMS guidelines etc. For example, the Declaration of Helsinki states that "*at the conclusion of the study, patients entered into the study are entitled […] to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits"* (World Medical Association, 2008). This position has been slightly adjusted in the new version of the Declaration of Helsinki (World Medical Association, 2013). Nonetheless, in line with this provision, we can infer that for-profit research sponsors that abide to this regulation by ensuring good access to proven medication to the host communities after trials are acting in accordance with universal justice

In reality, benefit sharing based on universal justice is not enough to resolve the problem of its practice. This is because most regulations on benefit sharing are not enforced into laws. Apart from the Nagoya Protocol on Access and Benefit Sharing in research involving non-human genetic resources, other regulations on benefit sharing in global health research involving human subjects take the form of non-binding international ethics guidelines. Moreover, some of the provisions on benefit sharing in the international ethics guidelines are vague, leaving some ambiguity in its practice. Consequently, we require the Aristotelian particular justice in order to shift benefit sharing from a realm of acting in accordance to legal regulations of benefit sharing to a fair sharing of research benefits among deserving research participants and communities. Under the particular justice, the for-profit research sponsors are expected to share research benefits to the host communities not necessarily because of the stipulated law, but because it is ethically good to do that. We elaborate on particular justice and show how it relates to benefit sharing in global health research.

Distribution of goods and benefit sharing

Just distribution of social goods can be achieved in a society if the principle of equality among deserving members complies with a *geometrical proportion* (Denier, 2007). A distribution in

accordance to geometrical proportion means that two individuals [or groups] have to be equal first before they can receive equal proportion of the goods. If the individuals or groups are not equal, then justice would demand that the less advantaged should benefit more on the shared goods than the most advantaged one. In order words equals should be treated equally and unequals, unequally (Young, 2006). For example, a government can decide to distribute radio sets to school pupils in order to encourage the practice of listening to the news. It will be unjust to give out only the radio sets to both pupils with normal hearing sense and those with impaired hearing because they are unequal in their hearing abilities. Justice will demand that the hearing impaired pupils should receive adapted support to compliment their hearing problem —say, sets of hearing aids (assuming that the use of hearing aids will enable them to listen to radio). This type of distribution of goods is in accordance with the principle of distributive justice. It is vital for a distributive justice principle to determine a criterion on which distribution of goods to the deserving groups should based on. Set criterion could be based on the *rights, needs, status or contribution* of the beneficiaries (Tornblom & Foa, 1983). In the example of distribution of radio sets to school pupils, the hearing impaired pupils deserve adapted complimentary benefits (hearing aids in addition to the radio sets) based on the criteria of *need.*

For-profit research sponsors ought to comply with the geometric proportion principle in the distribution of research benefits to communities in resource-limited countries. Many resource-limited countries live in poverty and compromised health care systems where health infrastructures are dilapidated or non-existent. These bad conditions have created a criterion of *need* for a distributive justice where for-profit research sponsors ought to share benefits to the communities where research is conducted. Furthermore, the need criterion of distributive justice has underscores the relevance of considering more benefit sharing practice in resource poor countries than communities in industrialized countries that mostly have efficient health systems and good access to healthcare.

In as much as distributive justice underscores benefit sharing in research, its arguments is weak for global health research collaboration across countries. This is because the distributive justice principle is centred on just distribution of benefits among individuals or groups within a nation

state (Van Parijs, 2007). As such, we require a platform on which benefit sharing can extend to citizens outside the geographical boundaries of a state. A global distributive justice argument fits well for such a platform. While distributive justice underscores just distribution of goods among individuals and groups within a state, global distributive justice extends and fortifies such just distribution of benefits to other people that are not within a national boundary or a state. In this reasoning, for-profit research sponsors are expected to uphold benefit sharing in global health research as a means of distributing health goods and services to resource-limited countries in order to improve their healthcare systems. Global distributive justice in health research has been advocated through benefit sharing. For example, the Human Genome Organization (HUGO) Ethics Committee—a committee set to deliberate on benefit sharing and other ethical issues in genetic research, has suggested that companies involved in international health research should set aside 1-3% of their profits for charitable work to improve the health care of populations in poor countries (HUGO Ethics Committee, 2000). Also, Ballantyne (2010) expresses the view that commercial research industries outsource research in developing countries because they enjoin surplus profits that they would otherwise not realize when research are conducted within an industrialized country. She then proposes that a global research tax should be set aside by the commercial research industries from the surplus profits which are meant for developmental projects in resource poor countries. This global research tax could be used to generate revenue for local health-related capacity building (Ballantyne, 2010).

Reciprocity in exchange of goods and benefit sharing

Aristotle further describes another type of particular justice whereby persons (or groups) freely exchange equal proportion of goods. The goods to be exchanged have to be proportionately equal and that the parties have freely agreed to embark on a reciprocal exchange of such good in a transaction (Aristotle, 2011). In Aristotle's example: *'let A be a builder, B a shoemaker, C a house, D a shoe. The builder, then, must get from the shoemaker the latter's work, and must himself give him in return his own. If, then, first there is proportionate equality of goods, and then second reciprocal action takes place, [then a just exchange is said to occur]. If not, the bargain is not equal, and does not hold; for there is nothing to prevent the work of the one being better than that of the other; they must therefore be equated'* (Aristotle, 2000; Pakaluk, 2005). The idea here is that if individuals or groups voluntarily transact and exchange their goods and

services with one another, for such transaction to be considered just, then the goods to be exchanged must be proportionally equal. This Aristotelian notion of exchange is also known as commutative justice or justice in exchange (Schroeder & Lasén-Díaz, 2006). Commutative justice is not concerned with the *equality* of the individuals or groups involved in the transaction, rather it is concerned with the *proportionate reciprocation* of the goods to be exchanged (Denier, 2007). However, in practical terms it is difficult to establish two things that are proportionately equal as not all goods are easily comparable. For example it may be difficult to correctly establish the number of pair of shoes that are proportionately equivalent to a house. Aristotle points out that money can help in solving such proportionate difficulties—because money is an intermediate that serves as a measure for all things. Money serves as a surety to get some goods that one needs and the amount one pays serves as the proportionate equality to the goods one needs(Pakaluk, 2005). This means that an exchange in a transaction that leaves one party with too little money than the right amount is said to have been *treated unjustly* and a party that has too much money than it is supposed to be in a transaction is said to have *acted unjustly*.

Commutative justice as it relates to benefit sharing fits well in non-human genetic research such as research involving the use of plant genetic resources as delineated in the CBD. The CBD regulation has granted property rights to the custodians of genetic resources(CBD, 1992). In other words the custodians of genetic resources have a sovereign right over the biological diversity (goods) within their geographical boundaries. In accordance to Aristotle's commutative justice, transaction between a local communities and a commercial research sponsors can only be just when plant genetic resources that the research sponsors obtain are proportionately exchanged with benefits to the local communities (De Jonge, 2010). The research sponsors can provide proportionate exchange of goods that the communities might need such as social infrastructures, technological transfer to the communities etc. According to Aristotle, money would be the appropriate medium that can measure the worth of biological resources. However, the use of money as incentives is highly discouraged in research—as such we advocate that research sponsors should endeavour to effect health and infrastructural development in communities in exchange for the biological resources they obtain from the communities.

Commutative justice argument for benefit sharing does not stand strong in benefit sharing in global health research involving human subjects, because human subjects do not have the property rights over their body to that extend that they can freely exchange their organs or tissue with other goods. As such, because the body cannot be seen as a property (Kirchhoffer & Dierickx, 2011), it is difficult to talk about commutative justice where researchers offer money or other goods to research participants in exchange with body materials for research. Moreover, human genetic resources have been removed from the legal framework of the CBD (CBD COP Decision II, 1995).

Correction of private transactions that have gone wrong and benefit sharing

Aristotle describes that private transactions among individuals or groups can sometimes go wrong whereby one party suffers harm and as such suffers an injustice. Such transactions can take the form of *involuntary or voluntary* transaction (Aristotle, 2000). In the case of involuntary transaction, the consent of one of the parties in the transaction is absent; as such the party that did not consent has been coerced or forced into the transaction. Involuntary transactions are carried out either in secrets such as theft, poisoning or in violent ways such as robbery, assault and insult. In the voluntary transaction, the parties involved in the transaction have voluntarily agreed to exchange the goods and services. For example, voluntary transactions are seen in trade transactions such as buying, lending at interest, pledging and letting for hire. Transactions in which one party has suffered an injustice need to be addressed through corrective justice or restorative justice. Corrective justice is mainly aimed at restoring equality between the injured party and the perpetrator of the injury. Corrective justice focuses on an *arithmetic proportion* in restoring equality to the injured party. This implies that parties involved in the transaction are considered equal entities—what matters is whether the compensations to the injured party are proportionate to the degree of injustice suffered (Denier, 2007; Young, 2006).

Research activities between participants and communities on the one hand and research sponsors on the other hand take the form of voluntary transaction because the groups have voluntarily consent to interact. In some cases, such research transactions can go wrong and the research communities and participants suffer varying degrees of harms. These harms could be as a result of unintentional occurrence or wrong ethical conduct by the research sponsors. For example,

unintentional occurrence could be that the intervention to be tested in the research have severe adverse effects on the participants such as in the Pfizer Trovan Trial (Ready, 2001). Wrong ethical conduct could be sponsors' over utilization of the existing local health facilities of the community for their research, or the sponsors' total reliance on the local health staffs for their research thereby curtailing the adequate provision of integrated health services to the population (Hughes, 2014). These conducts constitute forms of harm to the research communities and participants and requires some form of restoration. Aristotelian corrective justice or restorative justice is closely related to compensatory justice in the contemporary discourse of justice (Hill, 2002). Compensatory justice in turn, is linked to benefit sharing and is aimed at ensuring fair recompense to the research participants and communities in return for their contribution (HUGO, 2000).

An advantage of compensatory justice approach to benefit sharing is that, sharing of research benefit is not necessarily narrowed to the participants and communities in resource poor countries only but also in industrialized countries. This is because participants and communities in industrialized countries can be subjected to similar risks and burdens as their counterparts in developing countries. Ndebele argues this stating that:"*research participants from both industrialized nations and those from limited resource settings should be compensated equally since they suffer the same burdens and equally contribute towards the study by contributing the same product data"* (Ndebele et al., 2008).

Conclusion

While many publications on benefit sharing only mention the link between benefit sharing and Aristotelian commutative justice, this is the first paper that applies the broader concept of Aristotelian justice to benefit sharing in global health research. The paper has critically analyzed benefit sharing in Aristotelian universal justice and has provided the insight that benefit sharing within the universal justice would mean obeying the set rules and legal frameworks on benefit sharing. We have also broadened the analysis by evaluating benefit sharing within the three perspectives of Aristotelian particular justice. Among these three perspectives, we have demonstrated that distributive justice and compensatory justice offer a good justification for

benefit sharing in global health research. Commutative justice is not so suitable for benefit sharing in global health research involving human subjects because of the restriction on commodification of the human body. Nonetheless, the commutative justice approach might well be suited in research involving non-human genetic resources.

Accordingly, commercial research sponsors must endeavour to contribute to the development of health care system in resource limited countries. In accordance to universal justice, the research sponsors must abide by the international standards and legal frameworks on benefit sharing. However, because there are no legal frameworks on benefit sharing in global health research and the international guidelines are not well elaborated on the aspect of benefit sharing, universal justice is not enough to strengthen benefit sharing in health research. We need the Aristotelian particular justice which consists of the three ethical justifications of distributive justice, commutative justice and corrective justice. As such, it is important for commercial research sponsors to think of benefit sharing outside the box of legal frameworks. As Aristotelian justice is still relevant to the contemporary discourse on justice, this paper has broadened the ethical justifications of benefit sharing within the justice framework in global health research.

Finally, we must point out that the emphasis on benefit sharing on for-profit research sponsors does not necessarily exclude non-profit research organizations from the requirements of benefit sharing. The emphasis is prompted by the high possibility for self interest and exploitation of host communities in research by the for-profit research sponsors (Glickman et al., 2009; Petryna, 2007) compared to the non-profit sponsors. Nonetheless, non-profit research organizations should also uphold responsive research practices that are tailored to the health needs of resource-limited countries.

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Part 2: Empirical Research on the Concept of Benefit Sharing

Part Two Chapter One: An Ethically Accepted Concept but not well known: Research Ethics Committees in Nigeria on the Concept of Benefit Sharing

Based on:

Dauda, B and Dierickx, K: An Ethically Accepted Concept but not well known: Research Ethics Committees in Nigeria on the Concept of Benefit Sharing. *Journal of Clinical Research and Bioethic 6:226. doi: 10.4172/2155-9627.100022*

Abstract

Background: The concept of benefit sharing deals with the issue of what participants and communities ought to benefit from participation in research. There are few empirical studies that focus on the aspect of benefit sharing in clinical research. As such, this research examines the awareness and viewpoints of Ethics Review Committees in Nigeria on the current discourses related to the concept of benefit sharing.

Methods: Semi structured interviews were conducted with key stakeholders of selected Research Ethics Committees in Nigeria. Interviews were audio recorded, imported to NVIVO 10 software, transcribed and thematically analysed.

Results: Ten interviews were conducted with members of Ethics Committees in Nigeria. Respondents expressed different understandings of benefit sharing. They considered benefit sharing as a panacea for adverse drug reactions, financial gratification and as a means of disseminating research findings. They also highlighted different ways to achieve fair benefits in research, such as the inclusion of negotiations with community representatives and the use of benchmarks on research benefits. Furthermore, respondents favour the development of legal frameworks on benefit sharing in international research.

Discussion: Research findings indicate that benefit sharing is a well accepted ethical concept. However, it lacks good awareness among ethics committees especially when compared to the ethical concept of informed consent. The lack of awareness is analogous with the fact that there is a lack of a consistent definition among research scholars. A succinct and consistent definition is essential to boost global advocacy on benefit sharing. Furthermore, to improve good outcomes of benefits in research, efforts of the community representatives should be complemented with the expertise of ethics committees.

Conclusions: a good awareness on the concept of benefit sharing will help in improving its practice, improve its advocacy and set the pace for the development of a benefit sharing framework in clinical research.

Background

One of the key concerns related to international clinical research conducted in Low-Middle Income Countries (LMIC) is benefit sharing. Benefit sharing pertains to the questions of what participants, communities and even host countries should accrue for their participation in research (Schroeder, 2007). Research ethics scholars like Millum (Millum, 2011), Ballantyne (Ballantyne, 2008a, 2010), Schroeder (Schroeder, 2009) endorse benefit sharing as an ethically sound concept and support that something ought to be given to the participants and communities in research. Also benefit sharing has been considered to be one of the ways to promote the social value of research and contribute to the improvement of global health (Lairumbi, Michael, Fitzpatrick, & English, 2011).

However, the main concerns regarding benefit sharing include the question: what exactly should be given as benefits to research participants and communities? In other words, what *fair* benefits research communities should accrue as result of participating in research? Other concerns are the ethical justification(s) that benefit sharing is based on, and who are the right recipients of benefits? Authors have argued that these concerns do not impede benefit sharing as such. For example, regarding the question of what exactly should be given as benefits, proponents of benefit sharing have argued that fair benefits can always be negotiated between research sponsors and host communities (Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2004). With regard to the justification(s) on benefit sharing, we have noted elsewhere that different ethical justifications on benefit sharing do not necessarily weaken the advocacy of the concept in practice. The various justifications rather provide different platforms that encourage the practice of benefit sharing in international research. For example, a benefit sharing justification that is rooted in commutative justice envisages benefit sharing solely as an instrument of exchange. This is different from a distributive justice perspective that views benefit sharing as means of fair distribution of health resources with adequate consideration to the *need* of the least advantaged groups (Dauda & Dierickx, 2013). For the appropriate recipients receipts of benefits, researchers have advocated that research sponsors should engage the host communities in all the phases of research in order to identify the right groups that ought to benefit from research (Schulz-Baldes, Vayena, & Biller-Andorno, 2007).

While these arguments and counter arguments continue within the global ethics platform, little is documented on the perception of benefit sharing among research stakeholders in resource poor countries. Discourses on benefit sharing are often theoretical with little empirical inquiries on what the concept entails among research stakeholders especially in developing countries. For example a literature search to ascertain empirical studies that relate international research and benefit sharing reveals few publications. While some of the studies address the perception of stakeholders in a resource poor country on various forms of benefit sharing (Lairumbi et al., 2012; Molyneux et al., 2012), others have examined stakeholders' understanding and the state of debate on the concept of benefit sharing (Lairumbi, Parker, et al., 2011). Another study targets the research participants in South African communities to ascertain their perspectives on benefit sharing in international research (Zvonareva et al., 2013). This present study is the first empirical work that examines the discourse of benefit sharing among ethics committees in Nigeria. It identifies some key concerns on benefit sharing that could contribute to the development of a benefit sharing framework.

Aim of the study

This study aims at examining the awareness and viewpoints of Ethics Review Committees in Nigeria on current discourses of benefit sharing through an open-ended interview. The study does not aim at questioning in order to query the activities of the various ethics committees with regards to the concept of benefit sharing but to ascertain the familiarity of the concept among the ethics committee members.

Study setting and methodology

Study setting

The operations of the Ethics Review Committees (ERCs) in Nigeria are governed by a central National Ethics Committee known as the National Health Research Ethics Committee (NHREC). The NHREC was established in 2005 after the infamous Pfizer Trovan trial (Agunloye et al., 2014).One of the notable functions of this national body is to register, regulate as well as audit local ERCs in various institutions across the country. As such the NHREC maintains an up-to-date register of recognized ERCs in hospitals and research institutions in the country.

The study was conducted in Nigeria between June and July, 2013. To ensure that the potential stakeholders for the study are extracted from eligible ERCs in the country, we obtained an updated list of the registered ERCs from the NHREC website. As at the time of the research, nineteen Ethics Committees were found to be duly registered by the NHREC. We obtained the contact details of the various committees on the list with the intension of including all the registered Ethics Committees in the research. However, after efforts to contact the committees through telephone and email we were only able to reach fifteen committees. We could not reach four committees due to one of the following reasons: the telephone numbers were no longer functioning, the contact person no longer works in the institution or there was no email response from the person contacted. The fifteen committees that responded, an email was sent to explain further some practical aspects of the study. Ten out of the fifteen ERC responded with an affirmative answer for participation. These ten ERC were included in the study, followed up and subsequent arrangements on the study were made.

Study instrument: Semi-structured interview

The study utilizes a semi-structured interview. The interview questions were designed by the authors with good guidance from research literature on how to develop and prepare interviews for data collection (Doody & Noonan, 2013; Rabionet, 2011). The interviews were conducted in English and questions were open-ended, which allow the respondents to freely express their views. Also question prompts were used in the course of the interviews to ensure that respondents have clearly exhausted their responses to a question. Examples of question prompts used are: “can you think of more…”, “can you elaborate further on…”

The time and location for the interviews were arranged prior to the date scheduled. All the interviews were conducted in the respondents’ office where they are more relaxed and comfortable. The interviews were also conducted behind closed doors with no interruptions from external parties.

Consent Process

Before the start of the research interview, a document explaining the interview process was submitted to the Kaduna State Ministry of Health Ethics Committee. At the beginning of each interview, respondents were informed that the interview would be recorded and it will be kept

confidential, anonymous and will only be used for the purpose of the research. Participants were informed about the possibility to decline participation. Furthermore, they can decide not to respond to parts or whole of the questions or demand for the discontinuation of the audio recording. All this information was audio recorded and respondents were asked for their verbal consent before the interview was initiated.

Data analysis

The recorded interviews were imported into the NVIVO 10 software and were then transcribed. All the interviews were thoroughly coded. Four major categories were first created to represent the units of analysis of the interviews. Under each category, codes and sub-codes were generated based on the respondents' perspectives on the posed questions. The coding process was carried out independently by two coders. This double coding was done in order to validate the coding process and to ensure that the respondents' perception were exhaustively represented. The codes were then carefully verified and agreed by the two coders to ensure that they rightfully belong to the assigned major category. The codes were analyzed within the major categories using a content analysis (Elo & Kyngäs, 2008).

Results

The ERC members drawn for the interview had different health professional backgrounds which include Gynaecologists, Neurologist, Statistician, Microbiologist, Pharmacist and General Practitioners. The respondents also held different positions within the Ethics committee, nonetheless majority of the respondents are heads of their ethics committees (Table 1). Respondents were asked to mention some ethical concerns they encountered or perceived as vital in research involving human subjects. Informed consent and sound methodology were the most mentioned issues. Benefit sharing was not mentioned as an ethical concern. However when prompted to further elaborate on sound methodology, the respondents mentioned fair distribution of benefits and burden as some of the aspects that constitute sound methodology. Also, upon prompting the respondents indicate that benefit sharing is an important concept in research. We present the stakeholders viewpoints on benefit sharing in international research in four major categories: what is benefit sharing?, the process of achieving fair benefits, laws on benefit sharing in international research, and who gets what type of benefits?

Respondents	Sex of respondents	Respondents' position in Ethics Committee	Perceived vital concept in Research Ethics
1	Male	Chair of Ethics Committee	Very comprehensive consent document
2	Female	Chair of Ethics Committee	Safety issues/right to refuse participation Inadvertent use of hospital resources Study design
3	Female	Secretary of Ethics Committee	Scientifically sound research Comprehensive consent documents Methodology
4	Male	Chair of Ethics Committee	Objective of study/Methodology Informed consent
5	Female	Committee member	Scientific methodology Informed consent
6	Female	Secretary of Ethics Committee	Consent document CV of researcher Scientific quality
7	Female	Chair of Ethics Committee	Inform consent document Safety issues Scientific component
8	Male	Chair of Ethics Committee	Informed consent/respect for people Scientific validity and methodology
9	Male	Committee member	Informed consent
10	Male	Chair of Ethics Committee	Methodology/Aim and objectives Informed consent

***Table 1**: Demographic characteristics of respondents and perceived ethical concerns in research*

What is benefit sharing?

In terms of what benefit sharing concept denotes, respondents expressed different awareness on the concept. This awareness focuses on three major aspects: benefit sharing as a panacea for adverse drug reactions, benefit sharing as financial gratification and benefit sharing as dissemination of research findings

i. A panacea for adverse drug reactions

Benefit sharing is envisaged as something that ought to be put in place in order to cater for research participants in the event of adverse drug effects during the research. The idea by these respondents is that benefit sharing should be considered only when the need arises and it should not be a means of providing financial rewards to participants.

> *"It should not be viewed as financial gratification, definitely not. If during the course of participating something crops up, there should be provision made, to make sure that is not just glossed over or swept under the carpet. If the participants need to be treated say there is adverse reaction they should be taking care of, not just left on their own or seen as their problem."*

Financial gratification and incentives were also seen to be associated with the likelihood of inducements of participants which respondents unequivocally rebuffed in research. Respondents expressed a sense of indifference and discretion on advocating for benefit sharing acknowledging that benefit sharing concept may be prone to financial inducements in research.

> *"We do not really want to encourage it [benefit sharing] so that it would not serve as a form of financial inducements to participants. But all the same the participants also needed to be compensated."*

ii. Financial gratification

An opposing view from the financial inducements standpoint is the understanding that research sponsors ought to consider the inconveniences and burden they have placed on research participants. Such inconveniences should serve as the main drive to provide benefits in monetary terms to cover their transportation, food and in some cases monetary rewards to encourage participation.

> *"Assuming now in your research you state that when you recruit research participants and you will invite them again to come for a day when you need to collect their information. Of course in that case you are asking someone to come back. It is inconveniencing, so we now have to tell you please provide transport for these participants. We also check the time you are going to take for sample collection, person information and data, and now say why not provide them with lunch or other incentives."*

The need for financial rewards to participants was also viewed from a purely enterprising standpoint. Respondents indicate that research sponsors want to make financial gain with tested products. They envisage research activities as a big financial venture that would subsequently generate profits to the research sponsors. As such benefit sharing is basically a means in which research sponsors should give financial benefits out of their large profits to those that contributed to the success of such enterprise.

"Of course the source of the knowledge generated from research is the patient group that you use in the research. The information that you find out from them is usually plough [sic] back into your industry that are translated into drugs and other things that can now generate a lot of profits. So really it makes a lot of sense that if you are going to do research at international level then the patient and the community from which the patient come from need to also have some benefits out of it."

iii. Dissemination of research findings

Benefit sharing was also depicted as essentially a communication of all research findings by the researchers or sponsors to the research communities. Communication was thought to be a very vital *end product* of research and considered obligatory by all researchers. For these respondents, an effective way to ensure communities have benefited from research involvement is to disseminate the research findings at the end of the research.

"Well I think it has to do with the post study. Ideally from my experience in bioethics, if you are conducting a research in a community, after the research is over, you are supposed to share your findings with the community. That's how it's supposed to be, not for you to cart everything away."

Process of achieving fair benefit

Processes in which fair benefits in research can be achieved are highly talked about aspect in the discourse of benefit sharing in international research (London & Zollman, 2010). Respondents point out ways on which fair benefits can be achieved or what constitute fair benefits in research. These views are expressed in three specific categories: negotiations with community representatives, setting benchmarks for benefits and ethics committees to decide fair benefits

i. Negotiations with community representatives

The respondents note that the benefits of any research ought to be negotiated between the research sponsors and the host community. Respondents suggest that the host community ought to have some good representatives that should genuinely negotiate for what benefits best suit the community.

> *"I think this requires engaging the community and engaging researchers and sponsors. There should be a reflection of the culture in the particular setting. I don't think one rule should apply in all. So I think maybe if there are some recommendations like round table discussions and recommendations with some amount of variations. I should also say that the representatives truly represent the community. For example, the case of Niger Delta region [Nigeria]—although not related to research, but on the issue of what the oil companies are doing. Many of the representatives are not representing the community, they are representing themselves. So this really has to be people who truly have the best interest of the community at heart."*

However, other respondents expressed scepticism on the fairness of such negotiations considering the unbalanced negotiating power of the parties involved. These respondents believe that the negotiating power of most communities is usually weak compared to research sponsors. Such communities with weak negotiating powers would likely be taken advantage of by the research sponsors.

ii. Setting benchmark for benefits

Reflections on the process of achieving fair benefits were also thought to be feasible through the setting of a benchmark for benefits in research. This benchmark should serve as a standard on the basis of which research benefits can be assessed. A respondent noted that such benchmark can be deliberated, agreed upon and expressed as a percentage, which can then be applied to all research.

> *"I think there has to be a group or a body that should debate this and come up with a benchmark or a standardized position on benefits. They body [sic] could say 5 percent or 10 percent or 3 percent or whatever that group has decided let that be applied internationally. It should be something standardized, that if you do some research like this, it should be within the range of this to that percentage that should be the benefit. Just like*

we know in project management, we've been told that roughly one should spent about 10 percent of the total grant of whatever project one is doing on monitoring and evaluation- for instance. So we should have something like 5 to 10 percent or 1 to 3 percent. Let it be a standardized thing that you can always say okay what is the benchmark? Okay apply it, without even waiting for it to be debated or waiting for the beneficiaries to argue for it or fight for it."

Other interviewees think that whether or not the benefits of research should be sought for or negotiated depends on the type of research in question. In some types of research, participants have already some benefits through their direct participation. In that case, sponsors ought not to provide other.

"I think it will depend on the type of research. For instance, there are researches where the patients are already supported. I give you an example of HIV patients that we have on antiretroviral drugs. Researchers may want to do a survey on the knowledge or perception of a certain aspect of the disease. Those kinds of patients that are already been supported by the organization, the same organization wants to get more information from them. We will not insist on any extra benefit because participants are already supported with HIV medication."

iii. Ethics Committees to decide fair benefits

Owing to the growing awareness of the importance of ethics committees in assessing ethical aspects of research, respondents express the view that ethics committees should have the mandate to decide on the fairness of research benefits. Where the benefits outlined on the research protocol are inappropriate, the ethics committee can call the attention of research sponsors to correct and calculate what they deem as the appropriate benefits. Protocols that are assessed not to be beneficial to the participants or host communities can be rejected by the ethics committees.

"There was a research in which the committee felt so negative about. It was a situation where a non physician researcher was going to work with somebody in Obstetrics and Gynaecology to take some samples. We felt that even though the researcher was experienced enough, the benefit of that research to the patient was not sufficient and so we rejected the research protocol."

Legal framework on benefit sharing in international research

Asides benefit sharing in the context of plant genetic resources, which has a legally binding regulation, the concept of benefit sharing in international research involving human subjects is advocated as a non-binding regulation in existing research guidelines (Dauda & Dierickx, 2013). Nonetheless, some researchers advocate developing a legal framework on benefit sharing in international research. This section examines whether respondents would prefer benefit sharing to be legally regulated. This would mean that whenever research sponsors conduct research, they are obliged by law to provide benefits. Respondents were in favour of the establishment of laws on benefit sharing in research. For example one of the respondents expresses the need for a benefit sharing law relating the necessity of such law with the existing corruption in Nigeria:

> *"I really feel there should be a law. In this country [Nigeria], there is a lot of corruption and people like to cut corners. Even when there are laws people look for ways on how to evade from the laws, so how much more if there is nothing to hold them to. So without putting a law in place I am not sure there will be compliance in benefit sharing."*

A strong support for benefit sharing is also re-echoed from a standpoint that a legal backing on benefit sharing can serve as safeguard to ensure something gets to the host communities in research—otherwise sponsors would always do away with all the research benefits at the end of the research.

> *"Yes, the issue of benefit should be enforced, that's my candid opinion. Because there is no need somebody comes from the United States and conducts a research and goes away with all the benefits. It doesn't make sense, at all! There is no need somebody brings his drug from China and conduct a clinical trials in Nigeria and after that he goes back to sell the drugs in China without the participating community benefiting from it. There must be a law against these practices."*

A different opinion on the legalization for benefit sharing is that such legal promulgation would only create a situation where research participants would rush for the gains in research without having thorough reflections on the possible risks of the research. Respondents reiterate that benefits of research should never be considered above the risks or other unethical practices in research. In other words the fact that participants and communities would benefit from research can never be a sufficient reason to be unnecessarily exposed to research that is highly risky.

"I agree entirely that those who bear the burden of showing that your products are scientifically sound should also accrue a lot of benefits. But having said that, I think there should be a balance in this issue of law. You don't want a situation where once the words get out to the community that if a pharma company does research in your community, they must buy this and that and then people start allowing themselves to be subjects of research that is unethical, you know that these are vulnerable people."

Another reason why benefit sharing law should not be considered in international research is that researchers ought not to lose their autonomy. In other words, research sponsors ought to be trusted as self-conscious entities and ought to provide the right benefits of research to the host communities.

"Well it should be left to their own judgment of what they should do. They themselves (research sponsors) know the value of whatever research they have carried out and they should use the magnitude of their benefit to determine what to do in appreciation to the community. Maybe because we are a mission hospital we think people have conscience."

Who gets what type of benefit?

When speaking of benefit sharing, there is often confusion as to what it should exactly constitute. In this section respondents mentioned the various types of benefits they would recommend for research participants or communities. Furthermore, respondents are more inclined to believe that research benefits that target the community as a whole are to be preferred over individual benefits. However, they also emphasized the relevance of individual benefits.

i. *Benefits to the research participants*

The idea that research participants ought to receive benefits in monetary terms was again restated as a type of benefit to participants. Monetary benefits should accrue the participants because they would have to travel to the research centre or hospitals for appointments. However, there was a constant reiteration that such monetary benefit should not serve as inducements to participants. Making reference to a clinical research on HIV prevention, a respondent sums up:

"We have had instances where people wanted to collect data for Prevention from Mother to Child (PMCT) research. And in order to encourage participation, the participants were given some stipends. It's not like you are buying their consent but you know they will have

to travel down for the questionnaire and other data collection in the field. So you give them something to offset their transport."

Another idea that was mentioned is that the participation in research itself is a form of benefit to the participants. In the course of research, participants are likely going to benefit from the tested intervention (although in some cases they are harmed) or other forms of laboratory tests which may not be available or affordable to them in the absence of the research.

"Sometimes—for instance, the drug trials that we have done in the past, the provision of the medication to the participants we require them to be free of charge as well as running their laboratory tests throughout that period. That is also some benefits that accrue to them."

Respondents also envisaged that benefits to individual participants could arise from incidental findings during the research. When there are incidental findings whereby researchers have discovered something not connected to the research, participants could benefit from a treatment for such incidental findings:

"Like you could just do a study and part of the basic things you are asking for could be let's say for instance heamatocrit—the blood level of the patient and you discover that some of the patients are anaemic, you could make provision to help them to solve that problem that you found incidentally as a result of the study. That is a benefit to the participant."

ii. Benefits to the local community

Research benefits do not only entail benefits to the individual but to the local community as a whole. Respondents noted various forms of benefits that the community can benefit from hosting a research project. A well noted type of benefit is the reasonable availability of the tested medication at the end of the research. By reasonable availability, respondents are referring to making the proven intervention affordable or even free of charge to the research community. This reasonable availability should be plausible because the research sponsors would gain a monopoly of patency for a period of time and should afford to make the medication available at a subsidized price to the research community.

"You know when we are talking about drugs and private companies and patency, first when you produce those drugs you hold on the patency for quite a while and you make as

much money you can from it. The community that you have done the study might not have the strength to be able to benefit from that drug. And so it will be very important that such drugs are made reasonably available to such communities at a greatly subsidized if not free for people needing that medication within the community."

Other views included the idea of developing the local content. Development of the local content would involve research sponsors to look inward in the host country and see the feasibility of manufacturing the newly proven drug locally in the country. This would go a long way in subsidizing the medication and improve the living standard of the host country.

"For drug companies it will just be wise for them not to think about their side alone, but think about how they can improve the well being of the people. If you have conducted a research, you should ask for the manufacturing possibilities, does the country where the research is conducted have the raw materials, if they have the raw material or not you can bring them in and make arrangement to produce the drug locally."

Some suggestions are focused on the provision of facilities and upgrades of the equipment within the institutions where the research is conducted. This provision and upgrade of equipment can go a long way in serving the hospitals while in turn serving the people of the community.

"For instance if research is been conducted, by virtue of that research, the institution is going to acquire sub-zero deep freezers and laboratory equipment. Also—for example in your research you have to use a small clinic during the course of the research. Equipping it to a point where that is sustainable after you have left, those types of things you know are really important. We count that as important benefits to the hospital and to the community."

The idea of the provisioning of equipment in institutions is closely related to provision of basic amenities which was suggested by some respondents. They noted that research sponsors should link their research with a particular need of the community and endeavour to provide such need. For example, a respondent suggested that if a research sponsor is conducting a research on water borne disease, they can look at the community and provide for example say boreholes. This would alleviate the lack of potable water that is the main cause of the water borne disease in the community.

Benefit to the local community can also be achieved through capacity building of research and health staff. The local staff of the community hospital can be trained on how to use a recent technique or procedures in the laboratory or they can be offered scholarships on research methodology. Consequently the trained staff can in turn serve the community members for better health and research outcomes.

"There are supports that can be given to the representatives of the community by means of scholarships, this can help people from within the community to go and add knowledge which they can come back and plough back into helping the community."

"For me human capital development for the researchers is also very good, because you don't use people to get data for you without training them. It is wrong."

These indicate a benefit sharing that considers the whole community.

Discussion

By requesting respondents to identify some salient ethical aspects regarding research ethics, respondents consistently outlined informed consent or the necessity of a comprehensive consent document, sound methodology and research design as the main ethical issues that should be given due attention in research (Table 1). However when prompted on what sound methodology and research design entails, some respondents elaborate fair distribution of research benefits and burden as part of a sound methodology. In general respondents easily recognized informed consent as an ethical concept, whereas they had more difficulty in recognizing benefit sharing in that respect. This could be attributed to the fact that the issue of informed consent is highly discussed in international research ethics publications (Dawson & Kass, 2005; Jefford & Moore, 2008). The issue of benefit sharing however is not considered in great detail. Although the concept is recommended in ethics guidelines, it is often not adequately elaborated. In this respect, Johansen et al (Johansen, Aagaard-Hansen, & Riis, 2008) state that in most ethics guidelines the issue of benefit sharing is only superficially elaborated and as a result this is causing vagueness in benefits arrangements in research proposals. Similarly, the lack of a good stance on benefit sharing is reflected in the Nuffield Council Report on Ethical Conduct of Health Research in Developing Countries, which does not have a substantive statement on benefit sharing. The report simply notes that the issue of benefit sharing is outside the scope of

stakeholders and requires attention which would be addressed in the future(Nuffield Council, 2005).This indicates the need for a more robust advocacy that would place benefit sharing as a top ethical concept in research ethics practice

Similarly, respondents outlined different understanding and definitions of benefit sharing. While some of the respondents view benefit sharing from the perspective of financial obligations to the research participants, others have rejected the idea of financial incentives on the grounds that it may lead to participants' inducements. Yet, others view benefit sharing as obligations to cater for research participants in the event of adverse drug reactions. Also, financial reimbursements to participants for food, transportation and time spent in research participation were often expressed by respondents as benefit sharing. This is similar to an empirical study that research stakeholders envisage reimbursements as benefits as such creating a tension between the two concepts (Molyneux et al., 2012). In general, researchers have expressed reservation on whether the financial reimbursements should be regarded as benefit sharing (Kamuya et al., 2014). We concur with this reservation because financial reimbursements are more or less acts that aim at supporting participants to offset their expenditures as a result of their direct participation in research—rather than acts of benefit sharing (Ndebele et al., 2008).

Furthermore, the various understandings and definitions of benefit sharing indicate that the concept of benefit sharing in international research has no consistent or a succinct definition. Again, when one makes a comparison between *informed consent* and *benefit sharing* as concepts in research ethics, there is a marked difference in clarity of definition with the former having a more coherent definition than the latter. Such non-coherent definition of benefit sharing is highlighted by Schroeder in her effort to develop a precise definition for benefit sharing. She notes that most of the definitions of benefit sharing within human genetic resources are *either unclear or not definitions* (Schroeder, 2007). Furthermore, the non consistency in definition is reflected in the PUBMED database—one of the largest database for publications in medical sciences. A look at the MESH term for *informed consent* or *research design* or *intellectual property* reveal streams of definitions and meanings. Benefit sharing on the other hand, is yet to even have an entry as a MESH term in spite its long time usage in the international stage. This suggests that researchers have either been neglecting the concept or they cannot agree on a

consistent definition of benefit sharing for an entry as a MESH term. There is a need to review the existing ethics frameworks so as to give benefit sharing a consistent definition and due attention in international research. A clear and consistent definition of benefit sharing is necessary as this will set the stage of global harmony on the concept. Such global advocacy and harmony can be achieved if research actors are speaking on the same clearly defined concept. A clear definition is also necessary as this would ensure more awareness on the concept among various research stakeholders which would subsequently drive the development of frameworks and international good practice.

Respondents also outlined three major ways of achieving fair benefits for research participants and communities. The first method is through negotiations with the host communities that are genuinely represented by designated community representatives. That is to say, research sponsors should negotiate with the community representatives and agree on the terms of benefits for a research. This position is consistent with the fair benefit approach that has been suggested at the Conference on Ethical Aspects of Research (2004). The participants at the conference noted that only the host population can determine the value and appropriateness of the benefits to be proposed. Outsiders are unlikely to be familiar with the economic; social and cultural context and therefore unlikely to appreciate the importance of the proposed benefits (Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2004). The fair benefits approach has a very good appeal as it brings research sponsors and host communities in good research harmony and enhances community engagement, which has been highly advocated in international research (Kamuya, Marsh, Kombe, Geissler, & Molyneux, 2013). The second method that has been proposed by respondents is setting a benchmark for benefits such that research sponsors commit a certain percentage of their profits as benefits of research in the host community. This suggestion is analogous to the Human Genome Organizations' (HUGO) position on benefit sharing. The HUGO proposes that 1-3% of net profits by research sponsors should be set aside for obligations of health infrastructural development in developing countries(HUGO Ethics Committee, 2000). The third method suggested by respondents is that the ethics committees should hold the responsibility of deciding the benefits that suits the host communities. This position has also been recounted in existing literatures and research guidelines. For example, the WHO operational guidelines for Ethics Committees outline the role

of ethics committee in ensuring that the benefits and burdens in research are fairly distributed among the research participants (WHO, 2000). All the ways suggested by respondents are credible in deciding fair benefits. However, we suggest that bringing together the first and third methods would result in even better benefit sharing outcome. Ethics committees should be in close cooperation with the community representatives to work out benefits that suit the host community. A good liaison between the local ethics committee and the community representatives would result in a complementary exchange of ideas that would culminate to better and fairer benefits that reflect the need of the host community

Most of our respondents would agree to the development of a legal framework on benefit sharing. This is an empirical backing to our earlier publication where we suggest the need for a legal framework on benefit sharing. A law on benefit sharing would go a long way in strengthening its advocacy and practice (Dauda & Dierickx, 2013). Nonetheless, a few respondents express the view that poor participants would resolve to volunteer in unethical research if they know that they are protected by a law of benefit sharing. Other respondents assume that research sponsors should be trusted to provide benefits without been compelled by the law. These points are vital, but not sufficient to function as a counter argument to a law on benefit sharing. In the process of developing a benefit sharing law, these viewpoints can be considered and ways to address them can be carefully delineated. Furthermore, laws created for benefit sharing should be subject to constant review. For example, the bioethics laws in France have been subjected to regular reviews and updates since their adoption in 1994 (Berthiau, 2013). This would ensure a constant optimization and evolution of benefits as international research itself evolves.

One of the different ways respondents articulate as a form of benefit to participants is that individual participants would benefit from the medical care or even from incidental findings during a research. This claim maybe closely related to the problem of therapeutic misconception in research. Therapeutic misconception has been a well documented problem of research in developing countries whereby participants misunderstand the difference between the purpose of research and routine medical care (Mfutso-Bengo et al., 2008). Most studies documented on therapeutic misconception are on research participants and not on research ethics committees in

developing countries. As such, we cannot categorically infer that respondents' comments are unequivocally a case of therapeutic misconception. We suggest more studies to determine if the notion of therapeutic misconception exists among research ethics committees in developing countries.

Limitations of the study

The respondents in this study are recruited based on their willingness and subsequent availability for the interview. This has limited the variability of the study participants to only some regions of Nigeria. Considering the six geopolitical zones of Nigeria, we are able to get representatives from only three geo-political zones (North-West, North Central and South-East). The North-East region was not included because of the potential security risks as a result of insurgent activities. Although, we do not expect to have wide variation of responses with the inclusion of respondents from all the geo-political regions, nonetheless the study has limited generalizability to all ethics committees in the country

The views expressed by the respondents are mostly personal opinions and not the standpoints of the ethics committees they represent. This is because the ethics committees do not have written policy documents on benefit sharing and also show limited awareness on the concept. To this note, there is need for education on benefit sharing and other ethical principles in research among the ethics committees in Nigeria.

Conclusions

This study provides the first outlook of the perspectives of Ethics Committees members in Nigeria on benefit sharing in clinical research. The study has indicated a relatively low awareness of the concept of benefit sharing among the respondents. This does not necessarily suggest bad practice of benefit sharing in ethics review process among the respondents. More so, as indicated, the aim of the study is not to query Nigeria's ethics committees on benefit sharing but to know what committee members know about the concept of benefit sharing. Nonetheless, we are certain that a good awareness of the concept will lead to even better practice, improve its advocacy and set the pace for the development of a benefit sharing framework in clinical research. The findings of this study also suggest that benefit sharing has a wide scope as

respondents view it differently. While we agree that there could be various ways that benefit sharing can be perceived—we suggest however, the need to set a boundary of what benefit sharing should be (or should not). This is necessary, in order to have a definitive nuances on benefit sharing.

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Authors Contributions

The idea of the empirical study was conceived and developed by BD and KD. Both authors contributed equally to the first drafted manuscript. BD elaborated the various stages of the manuscript with thorough revision, editing and mentoring from KD during the pre-publication process. Both authors read and approved the final version of the manuscript.

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Part Two Chapter Two: "*When you work with the socio-economically disadvantaged populations, it is easier to exploit them.*" Perspectives of Research Stakeholders in Europe on Benefit Sharing in Global Health Research in Resource-Limited Countries

Based on:

Dauda B and Dierickx K. "*When you work with the socio-economically disadvantaged populations, it is easier to exploit them.*" Perspectives of Research Stakeholders in Europe on Benefit Sharing in Global Health Research in Resource-Limited Countries. *Submitted*

Abstract

The conduct of health research in resource-limited countries has immense importance in the improvement of public health. However, the conduct of research in resource-limited countries is often flawed by ethical and logistical challenges. One of the ethical challenges that until recently has started receiving attention is benefit sharing. Benefit sharing is a concept that refers to the act of given something in return to the participants and communities that contribute to a research activity. While the concept has been endorsed as an important concept in research, it is not well explored among the various research stakeholders involved in global health research. This paper examines the perspectives of health research stakeholders in Europe that are involved in research in resource-limited countries. We conducted semi-structured interviews with 11 respondents drawn from pharmaceutical companies, academic institutions and non-governmental organizations in Europe that are involved in research in developing countries. The respondents expressed different views and understanding on the concept of benefit sharing. Some of the views on benefit sharing include: an activity of partnering with research participants and capacity building of research partners. Respondents also expressed their viewpoints on the justifications or reasons for benefit sharing as well as legal framework on benefit sharing in global health research. Furthermore, respondents outlined organizations' corporate social responsibility as a reason for benefit sharing. In general, research stakeholders are well conversant with the nuances of benefit sharing—even though they expressed different understanding on the concept. We suggest more research on the link between Corporate Social Responsibility and benefit sharing.

Keywords: Benefit Sharing; Post-study benefits; Research Ethics; Medical Ethics, International Clinical Research

Introduction

Health research conduct in resource-limited countries is of immense importance in the improvement of public health. This is because health research serves as a driving force through which we can understand the pathophysiological processes of diseases, epidemiological patterns of disease transmission and map out public health interventions to control them (Dauda & Dierickx, 2012). In addition, health research such as clinical trials helps in developing drugs and other therapeutic interventions which are relevant in secondary prevention of diseases in patients and populations. Nonetheless, the conduct of research in resource-limited countries faces numerous challenges ranging from ethical to logistical. Examples of these challenges could be the issue of how to obtain a good informed consent or the difficulty to maintain a cold chain for a trial medication. The challenges are easily noticeable because of the unique socio-cultural background as well as the low economic status of people living in these countries (Calman, 2002). Research sponsors from developed countries are recommended to consider these challenges and endeavor to offer solutions whenever they conduct research in resource-limited countries (Glickman et al., 2009). While some of the challenges have received adequate attention, others until recently have started to attract particular attention in research. For example, the ethical challenge of how to obtain good informed consents in research in resource-limited countries has received adequate attention. This is evident in literature reviews and empirical studies that focus on ways to improve informed consent in research in developing countries (Thanh Tan et al., 2015).

One aspect of the ethical challenges that until recently has started receiving attention is the potential for exploitation in research in developing countries (Munalula-Nkandu, Dierickx, Munthali, & Viofora, 2012) and the need to provide research benefits to participants and their communities (Molyneux et al., 2012). Exploitation in research refers to a situation where the research participants and communities receive un*fair benefits* from their engagement in research activities with the research sponsors (Gbadegesin & Wendler, 2006; Resnik, 2003). Exploitation has been shown to be unethical in research, and to curb against it, research stakeholders must improve the ethics of benefit sharing (Resnik, 2003). Benefit sharing deals with the issue of what research participants and the communities ought to benefit or gain as result of participating in

research. It is widely accepted that research should answer the health need of the host country and that the participants should be entitled to the share of benefits emanating from the research (Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2004). However, there are still some unresolved issues associated with benefit sharing. These include the precise definition of benefit sharing in global health research as well as what exactly counts as fair benefit to the participants and host communities in research (Schroeder, 2007). Researchers have also noted the concern on the right recipients of research benefits—whether is the individual participants or the wider communities (Lairumbi et al., 2012). Another concern is related to the justifications for benefit sharing in global health research— whether it should be based solely on ethical principles or there should be additional justification from a legal standpoint (Dauda & Dierickx, 2013).

These unresolved issues are the main impetuses for this present study. This study examines the fundamental issues related to benefit sharing among stakeholders in Europe involved in global health research in resource-limited countries. The central aim of this study is to assess the perception and experiences of these research stakeholders on benefit sharing in global health research.

Context and methods

This study is the second of a two part empirical study that examines the concept and practice of benefit sharing in health related research in resource-limited settings. The first part of the study assessed the perspectives of Ethics Review Committees with a target on a resource-limited country (Nigeria) as an example. This present study builds on a similar focus as the first but with different study respondents. The study respondents are stakeholders in pharmaceutical companies, academic institutions and non-governmental organizations within Europe involved in health research in resource-limited countries.

Data collection

The study is based on 11 semi-structured interviews conducted with respondents drawn from key persons in pharmaceutical companies and academic institutions as well as non-governmental organizations involved in global health research in resource-limited countries. The respondents were selected through a snowballing method whereby the first respondent identified led us to the

next respondents and so on until a point of saturation is reached. The point of saturation is when additional interviews with respondents no longer present new or relevant information that are different from the previous respondents (Bowen, 2008). Respondents were first contacted by email and when they agreed to participate in the research, practical arrangements were made for the interview. Depending on the location of the respondents, the interviews were either conducted face-to-face or through Skype calls. All interviews were fully audio-recorded and saved in a file. The respondents hold different positions and roles from the pharmaceutical companies, academic institutions or non-governmental organizations they represent, however, they were all actively involved in the conduct of research in resource-limited countries. Respondents compose of eight males and three females and they originate from six European Countries (Belgium, France, Italy, Spain, Switzerland and the Netherlands). Other characteristic profile of the respondents is presented in Table 1.

Data analysis

The audio-recorded interviews were transferred to NVIVO-10 software and then transcribed. Data analysis was immediately performed after the transcribing process. The analysis was performed using thematic analysis whereby key themes on the interviews were identified by the

Respondents	Type of Research organization	Research unit of respondents within organization
PH1	Pharmaceutical company	Corporate Social Responsibility
PH2	Pharmaceutical company	Clinical Research Development
PH3	Pharmaceutical company	Clinical Development & Regulatory Affairs
PH4	Pharmaceutical company	Access to Medicine
PH5	Pharmaceutical company	Clinical Development
AC1	Academic institution	Clinical Trials
AC2	Academic Institution	Public Health
AC3	Academic Institution	Parasitology
AC4	Academic Institution	Public Health and Prevention Medicine
NGO1	Non Governmental Organization	Neglected Tropical Diseases
NGO2	Non Governmental Organization	Clinical Trials

Table 1: Types of research organizations and research units of respondents

two authors. Identification of the key themes were guided by some of the current discourses on benefit sharing as revealed by the literature review that was earlier published (Dauda & Dierickx, 2013) and from the interviews. Based on the key themes, coding was performed by the two authors and the differences in coding were resolved through discussions and referring to the transcripts.

Ethics approval

The study does not require ethics approval from the ethics committee since it involves adult professionals. There is no any ethical obligation in Belgium for ethics approval for such research involving adult professionals. Nonetheless, prior to the schedule of each interview, we explained in detail the aim of the research interview to the respondents and they were allowed to decide whether they want to participate or not. Also, prior to the commencements of the interviews the respondents were allowed to decide if they want the interview to be audio-recorded. Verbal consents were requested and given by the participants before the start of the interviews.

Results

We present below, the stakeholders' perspectives on the various aspects of benefit sharing based on three major themes. These themes highlights some of the current debate on benefit sharing related to global health research in resource-limited countries

Meaning and scope of benefit sharing

An exploratory question on the meaning and familiarity with the concept of benefit sharing in global health research indicated that on all occasions the respondents were fully aware of benefit sharing. They also presented different views on what they would define benefit sharing as. Some of the respondents also elaborate on the scope of benefit sharing by explaining on what benefit sharing should or should not include. The following three categories capture the respondents' understandings on benefit sharing

Partnering and benefitting in research activities

Benefit sharing is envisaged as a way of partnership among various stakeholders in a research activity whereby the different groups that contribute towards achieving a common goal are treated fairly with respect to benefits. The following quote by an academic researcher underscores this viewpoint:

> *"If we do an activity, we have different people and different groups cooperating towards an objective. I think benefit sharing is when there is a common objective and everybody should benefit from that result according to their need. You have to talk about benefit sharing where you have common objective but really different partners and different needs. So the needs are different and so the benefit should be different."* [AC1]

This understanding of benefit sharing as partnering in research was again emphasized by a pharmaceutical company researcher. The respondent emphasized the need to respect the people in research and ensure fairness in benefits:

> *"I think benefit sharing is largely about respect for people and it's largely about working in partnership with people on a needful footing. If there is no fair level of benefit sharing then you may be profiteering from somebody's weakness. There is need to give and take and need to be fair for everybody in a research partnership."* [PH4]

Capacity building

Some respondents view benefit sharing as basically an opportunity to build capacity in resource-limited countries by empowering researchers in those regions to conduct their own research. An academic respondent stressed that benefit sharing does not necessarily mean benefit to the direct research participants but rather capacity building to the local research partners:

> *"In my personal point of view, benefit sharing is to share the knowledge not necessarily with the people we have investigated but with the people who we do the research with, that's what I call capacity building. For me, capacity building is an indirect way of benefiting the people who have contributed to the study [...]. I think knowledge, science, academic progress in itself is a virtue and that's what I hope I can achieve, not now not tomorrow but in the long term. It maybe remote from what you call benefit sharing but it's the most realistic one."* [AC2]

Other respondents did not restrict the target group for capacity building to the local research staff only, but something that should target all research stakeholders as well as the healthcare system of the host community. A pharmaceutical company respondent envisaged benefit sharing as that:

"*which would enable the persons that participated in international research to continue to have access to educated health care professionals, health infrastructures and diagnostic tools to have a better life."* [PH1]

An exchange in a research activity

There were also respondents who provided some understanding of benefit sharing as an exchange between research sponsors on the one hand and research communities on the other hand. The understanding of exchange is stemmed from the fact that the research sponsors usually gain from research outcome and ought to give back some benefits in return to the research community. This NGO respondent noted that:

"From my point of view benefit sharing is the benefits that the people where you are performing the research receive from the research. This is because the company obviously benefit from the data they get that is needed to license their product. Sharing benefit means that the population where trial is performed need to also have some benefit from the research." [NGO2]

When asked to briefly explain what benefit sharing in research meant to their research organization, one of the participants stated that:

"If something is gained in research then something should be given back to the local community because you have worked with the community. There should be emphasis to make the community better." [PH2]

Scope of benefit sharing

With regard to the scope of benefit sharing, the respondents explained that benefit sharing can cover a wide range of things that could be directed to the research participants or something to the whole community as explained by the respondent from an NGO:

"A patient enrolled in a trial should sometimes get direct benefit from the trial or the

community with information gathered through the patient participation will get some kind of benefit with the overall objective of the research." [NGO1]

In terms of what benefit sharing should include, most of the respondents express caution with regard to money as a form of benefit to the research participants. The caution with regard to money as benefit is mostly related to the possibility of inducing or coercing the research participants to participate in research as explained by this respondent:

"I am against the compensation of the patient for the participation in research because this is something that can really force people to participate in clinical trials due to the fact that they have no money for their family. We absolutely want to avoid any kind of forcing the people to participate and we never offer money for participation." [PH3]

To further explain the caution on money as benefit, respondents differentiate money given as compensations for time spent, effort, transportation etc during research participation with the actual benefits for participation in research. This difference is highlighted by an NGO respondent:

"*Benefit sharing is when there is something additional. The reimbursement or compensation is just giving back what has been spent or what has been lost because of the research, in terms of lost of work due to research participation. Benefit sharing has to be understood in terms additional things the research brings to everyone and to the patient."* [NGO2]

Reasons and contextual emphasis for benefit sharing

Reasons and justifications for benefit sharing is one of the major concerns in the discourse of benefit sharing in global health research. The respondents were asked to explain briefly the main reasons why they consider benefit sharing in their research activities. Most of the respondents' viewpoints were captured in two main categories:

Justice

Most of the respondents express the view that justice is the main reason why they consider benefit sharing in their conduct of research. Justice is emphasized from the point of equality and fairness to the research participants and communities that contribute in making research possible. This academic institute respondent viewed the justice reason from one of the institute's cardinal

missions of research conduct:

"I will first refer to justice [...] the philosophy of our institute for the cooperation programs is known as switching the poles. Switching the poles means cooperation of equal sides and overcoming the gaps in healthcare, but there are still gaps in access to health and research. So our main reason for research is really based on justice which connotes that everybody should have the same access to health." [AC1]

Other respondents, envisaged benefit sharing as an obligation rooted in justice whereby reciprocity is required when someone has giving something. This analogy is demonstrated by a pharmaceutical company respondent:

"It's an obligation that is motivated by the fact that data giving you the possibility to learn about the drugs and pathologies etc. It's a sort of obligation to give also the results of those research to the people. Someone that is performing clinical trials will have to take into consideration that they only succeed because of the participation of these people in the trial otherwise they cannot reach the goal to have the results of the study and to better understand if a drug is good, safe or not." [PH5]

Corporate Social Responsibility (CSR)

Respondents have also accounted that benefit sharing is carried out based on the organization's corporate image in the society or corporate social responsibility. This position is mostly stressed by the respondents from the pharmaceutical industries. For example, a respondent from the pharmaceutical company stated that:

"The health value creation or benefit sharing ambition of our company is centered on Corporate Social Responsibility for patients affected by diseases in the domain for which we are considered to be world experts [...] We have now done up to 7 projects in the world, which is not lot but it offers us a tool box to understand the hurdles and difficulties when you want to bring treatment, diagnosis and education to patient living in remote area in China in Africa, etc. So the benefit sharing we do is based on the arm of the CSR." [PH1]

Research conducted by academic researchers is thought to have intrinsic social responsibility to the society in itself; as such the research conduct is accompanied with the social responsibilities that improve the societal needs. This is expressed by a respondent from the academic institution:

> *"In the academia this very straight forward, if you do research the social responsibility is intrinsic, otherwise you wouldn't do research on malaria which affects the poor. We are an operational organization that wants to achieve an immediate impact on the health of our target population so that also mean for operational research that we do research that can answer immediate question from our team in the field to improve patient management, patient outcome."* [AC4]

Contextual emphasis for benefit sharing

With regard to the contextual emphasis on benefit sharing, all the respondents irrespective of their research organizations said that benefit sharing should not be emphasized only in resource poor countries but should be expanded to the developed countries. A pharmaceutical company respondent expressed this:

> "*Well I think it's a universal thing, it's not about developing countries only. If you have studies done in Western Europe, and you don't aim to share benefits with the community or the person, then I don't think it will work. The demands and the impact in developing countries will be bigger no doubt […] In the event that benefit sharing or value creation is hardwired into the genome of the company then it becomes a given for everyone in every place not only restricted to low and middle income countries."* [PH1]

A slightly different idea from the contextual look is stated by an academic researcher who emphasized the need to look at the vulnerability of a population instead of country per se. This respondent stated that:

> *"Maybe rather than talking about developing countries, I will talk about vulnerable population, but including socio-economic vulnerability. When you work with the socio-economically disadvantaged populations, it is easier to exploit them. So I would say the minority, including the social exclusion like homeless, undocumented migrants and that will include groups in rich countries. But majority unfortunately will include people in developing countries."* [AC1]

Legal frameworks and ways to strengthen benefit sharing

Legal framework on benefit sharing exist only in research involving the use of non-human genetic resources (Nagoya Protocol, 2010). In global health research involving human subjects, benefit sharing is advocated in non-binding international ethics guidelines with no legal framework. There has been debate whether legal framework for benefit sharing should be formulated for global health research (Schroeder & Lasén-Díaz, 2006). Most of the respondents expressed their reservation or doubt if a benefit sharing legal framework would work in global health research. They shared different viewpoints on their reservation and suggested ways to strengthen the benefit sharing practice in global health research

What benefit to include in the law

The respondents expressed that it will be difficult to develop a law without specifying what to be included in the law and at the same time it will be difficult to generalize exactly what should be considered as benefits in research. A respondent from the academic institution highlighted this by stating that:

> *"The problem is you have to specify that something in the law. I mean if you don't specify what the research sponsors should give back then the law will be useless, just an empty shell. On the other hand if you specify too much to give then I am afraid the pharma companies may be reluctant in doing research in that countries and this would boomerang back to the local communities. There would be less better [sic] health care, less capacity building."* [AC3]

A legal framework will discourage research

Other respondents expressed doubt on benefit sharing law based on the reason that legal framework will discourage conduct of research in resource-limited countries. A pharmaceutical company respondent expressed this fear and cited an example of research experience in an African country:

> *"This can be very risky unless you are the only country where such a trial can be performed. If you force by law to provide certain benefit, you risk the tendency of the research to go somewhere else. So in my opinion every country where there are strict laws*

of clinical research discourages big companies to go for research. That's my experience in Ethiopia for example, a country where there is lots and lots of regulations of clinical research and literally, they're performing three trials per year, unless if the situation has improved in the last years this was the case 5-6 years ago. So I think this is not positive for the countries because the research brings a lot of positives." [PH3]

Few respondents expressed a different view that there should be a legal framework on benefit sharing. One of the respondents from the pharmaceutical company feels that a legal framework is necessary to distinguish basic research from small academic research institutes and research sponsored by big commercial pharmaceutical companies:

"Yeah I think there should be a legal framework on which at least immediate or future benefits are made clear. This is because there is also a lot of basic research that is just answering academic questions not having any intention of eventual proven medication for people in developing countries. I think that it will be a fair question of government that they say well is good if you do clinical research in my country in order to develop a new drug but if later this drug will be inaccessible to a patient because of high cost, what is then the benefit to us? Why should we let you do the research? So I think there is a justifiable legal aspect that you can demand from a pharma industry that do clinical trials to make sure that the outcome of the research been it a new drug will be accessible and affordable later on." [PH5]

In terms of how to strengthen benefit sharing. The respondents that opposed the development of a legal framework suggested ways to achieve good benefit sharing practice in global health research. One of the pharmaceutical companies' respondents indicates the need to establish mechanisms to strengthen CSR among companies which go a long way in strengthening social responsibilities of companies in general.

"*I would hope that ethics prevail, but I know that is not always the case […] But the EU has issued a recommendation that CSR activities need to be reported in the annual report. Sometimes people are very reluctant but if you look at the Danish constitution for example, there is now for the most advanced CSR, obligations that every company follows. They have initiatives for local communities as well as for international communities."* [PH1]

Other respondents feel that to strengthen benefit sharing would require the encouragement of

communication between the research sponsors and the regulatory bodies as well as the ministry of health in the host countries. Such communication would encourage fair agreements and host country involvement in research:

> *"I think in my opinion, it should be an agreement. So, me as a company I come with a proposal for a certain research and we can find an agreement together, this is what I can offer, this is what is expected from you and little by little you come to an agreement that finally should be approved by the regulatory, by the ministry of health in some countries, by the ethics committee. So that's the way I see it, more of an agreement within scientist rather than regulators forcing some kind of benefit."* [NGO1]

Respondents also expressed the need for continuous training and education of research stakeholders and ethics committee on how to achieve fair benefit rather that creating laws:

> "*I think it is also good to invest in the awareness for ethical committee, ministry of health and people reviewing protocols. So if a country wants to increase this access or benefit sharing they can better train their people who are supposed to review the research proposals rather than writing laws. It will be a nightmare performing trials in certain countries because regulations are too discouraging. So I suggest they invest in training their people so they can make reasonable proposals to pharma companies, which most of the case in my experience are open to accept reasonable proposals."* [AC4]

Discussion

The different aspects of benefit sharing presented in this paper are part of the key issues in the current discourse on benefit sharing in global health research. The paper presents the different facets of the benefit sharing from research actors in Europe involved in global health research in resource-limited countries. Most of the empirical studies conducted on benefit sharing target researchers and participants in developing countries (Kamuya et al., 2014; Lairumbi et al., 2012; Molyneux et al., 2012). This empirical study offers a different viewpoint by focusing on the research stakeholders in developed countries that are involved in biomedical research in developing countries. The mixture of different respondents from the pharmaceutical companies,

academic institutions and NGOs is to ensure that different voices of research organizations are included in the study. It is noteworthy to state however, that we did not notice differences in the pattern of responses across the different respondents. In other words, differences in the organizational origin of the respondents did not influence the way they responded to the questions. This study provides a good insight and steers the need for more specific research on the different aspects of benefit sharing among research actors in developed countries involved in research in resource-limited countries.

We have noted that respondents are well conversant with the concept of benefit sharing in research. However, there were different understandings as to what benefit sharing entails in practice. Befit sharing was envisaged as partnering with research communities, capacity building for local health researchers and exchange between sponsors and communities. These viewpoints are consistent with the research ethics literature which mentioned these elements as part of benefit sharing in research. For example, Schulz-Baldes et all (2007) maintain that research capacity building is a good approach to ensure benefits to the communities and to reduce exploitation in research (Schulz-Baldes et al., 2007). Similarly, community engagement has been advocated in research because it encourages relevant research that are culturally and practically acceptable and ensures fair distribution of research benefits (Tindana et al., 2007).

With regard to what should count as benefit sharing, respondents indicate that benefits can be in form of goods and services to the participants and communities. This is also in line with another empirical study that highlights a range of different preferences of benefits that respondents would want to accrue in research. The benefits include those that are targeted towards the individual participants as well as the entire community (Lairumbi et al., 2012). The respondents also agreed that monetary compensations should be done with caution because of potential participants' inducements. This is in accordance with the argument expressed in many research ethics literature against monetary payments. The argument against monetary compensation is centered on the premise that money may serve as inducements which may cloud participants' assessment of the risk of research participation (Grady, 2005). It is important to first differentiate between compensations/reimbursements on the one hand and payment of participants on the

other hand. Compensations/reimbursements are acts done in order to make up for loses or cost incurred by the participants in the course of participating in a study. (Ndebele et al., 2008). Payments of participants are mostly employed in order to facilitate recruitment and participation in research (Savulescu, 2001). While we agree that sponsors should fairly compensate and reimburse participants during research, we do have some reservation on monetary payments to encourage participation. Monetary payment should be proportionate to research and caution should be used to curb against possible inducements of participants. However, the argument for inducements should not be used as an alibi for using participants without returning any benefits which can sometimes be in form of monetary payments. In other words sponsors should not hold back benefits because they are too cautious not too induce the participants. This view is based on the argument put together by Ballantyne (2008) that restricting payments to trial participants on the grounds of potential undue inducement provides more benefits for the research sponsors and reduces the financial welfare of the research subjects (Ballantyne, 2008a). Furthermore, Savulescu (2001) provides a plausible analysis why research sponsors should provide monetary payments to participants in research projects (Savulescu, 2001)

With regard to the justifications or motivation for benefit sharing, respondents expressed the views that benefit sharing should be based on justice and Corporate Social Responsibility (CSR). The mention of justice is envisaged to be associated with the broad meaning of the term—i.e. the fairness in the distribution of benefits and burdens that persons or groups deserve as a result of their particular circumstance and interaction with others (Beauchamp & Childress, 2009). However, justice as a reason for benefit sharing has to be viewed from the different perspectives of principles of justice. Each principle of justice produces a different benefit sharing rationale from another. For example, from a commutative justice principle, benefit sharing is viewed as an instrument of exchange. In this perspective, a benefit allocation in a given research interaction is considered *fair* only when there is an equivalent exchange between the research sponsors and the researched community. The inequalities of the parties involved in the exchange are not considered in the transaction. In the case of distributive justice principle, benefit sharing is rather a fair distribution of research benefits whereby the inequalities of the parties involved in the transaction are considered in the interaction (Denier, 2007).

CSR is a business management concept that is growingly employed by corporate organizations. The core concept of CSR entails integrating social, environmental and ethical concerns in companies' business operations and interactions with their stakeholders. CSR is generally understood as a way of achieving a balance in a company's economic, environmental, ethical and social imperatives (UNIDO, 2002). Leisinger (2008) distinguishes three dimensions of social responsibilities of a corporation to the society. These dimensions represent the levels of responsibilities that corporations operate in a CSR activity. They are the "must" dimension, the "ought to" dimension and the "can" dimension. The "must" dimensions are social responsibilities that are non-negotiable and the corporations are obliged by laws and regulations to carry out such responsibilities. The "ought to" dimension represents those responsibilities that are expected from any good corporation even where the laws are weak or absent. The "can" dimension denotes the voluntary assumption of additional responsibilities according to a company's capacity (Leisinger, 2008). Although Leisinger has not linked CSR to benefit sharing, we are of the opinion that a thorough investigation of the three dimensions of the CSR concept would reveal a good conceptual link with the concept of benefit sharing in global health research. We suggest more research to determine the normative ethical reasoning of CSR and to see how the core elements of the concept are linked to benefit sharing

Our research findings also point to the fact that the respondents thought benefit sharing should not only focus on research in resource-limited countries but also in developed countries. This finding is relevant considering the relatively strong advocacy of benefit sharing in research in developing countries which is mostly motivated by reason of poor socio-economic status of the populations and the weak healthcare systems (Hughes, 2014). However, in our research findings, respondents expressed that if benefit sharing is a good ethical concept—then it should be applied universally and should not be dependent on the context. The findings correspond with the debate put together by Barclay (2008) that: "*if one believes that some form of benefit-sharing is morally obligatory in research conducted in developing countries, it is very hard to escape the conclusion that it should at least in some circumstances be thought equally obligatory in research conducted within the borders of developed countries"*(Barclay, 2008).

With regard to the legal framework on benefit sharing, our research findings and those of an earlier empirical study we conducted with Ethics Review Committees in Nigeria (Dauda & Dierickx, 2015a) suggest a difficulty in determining whether benefit sharing in global health research should be formulated into a legal framework. While many of the respondents did not support the development of a legal framework on benefit sharing, some respondents present some seemingly good reasons for a legal framework on benefit sharing. We suggest thus, a critical look at the pros and cons as well as the feasibility of developing a legal framework on benefit sharing. However, we also suggest—as a starting point towards developing a legal framework, a strengthening of benefit sharing wording on the international ethics regulations guidelines. Strengthening of benefit sharing wording include an explicit statement on how to provide benefit sharing, who should be responsible for benefit sharing etc. An explicit wording on benefit sharing in ethics guidelines would be essential and help in guiding the developments of a legal framework global health research.

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Part Three: Normative Ethical Reflection on Benefit Sharing

Part Three Chapter One: Towards a Benefit Sharing Recommendation for Research Stakeholders Involved in International Research in Resource- Limited Countries

Based on:

Dauda B and Dierickx K. Towards a benefit Sharing Guide for Research Stakeholders Involved in International Research in Resource- Limited Countries

Abstract

This paper provides a benefit sharing recommendation for research stakeholders involved in international research. The paper starts by explaining the concept of benefit sharing with a spectrum of transactional exchange. This spectrum of transactional exchange explains benefit sharing in relation to the concepts of fair exchange, exploitation, gifting and robbery. We established that benefit sharing based on the spectrum benefit sharing has a normative bearing in research. We have also described three categories of benefits that participants and communities could be entitled to in a research namely: direct, indirect or collateral and aspirational benefits. Our benefit sharing recommendation is built on these categories of benefits and three fundamental questions for research sponsors that embark on conducting international research. Based on these three fundamental questions and the categories of benefits, we suggest the appropriate benefit sharing that should accrue to participants and communities in research.

Introduction

There is a general ethical notion that it would be unfair if a commercial research sponsor from a rich country went into a poor country, conduct research with the local people and generates a marketable product with huge revenues without giving something back to the poor country (Berg, 2001). Intuitively, in Kant's categorical imperative, a company, persons, organizations or any other entity should not use others as mere *means* without making them an *end* in themselves. The act of giving something back to individuals, communities or country where research is conducted is embedded within the ethical concept of benefit sharing. The concept of benefit sharing has a good ethical appeal and acceptance among research actors in international health research (Simm, 2005). Notwithstanding, the concept has unresolved issues within its nuances. For example, it is inconclusive as to what constitute the appropriate benefits that should be given to research participants and communities (Lairumbi et al., 2012). Furthermore, a look at the concept of benefit sharing among research stakeholders indicates that the concept is not well recognized in practice even though it is regarded as a good concept (Dauda & Dierickx, 2015b). Similarly, an empirical study conducted in Kenya reveals that some research stakeholders are not well familiar with the term benefit sharing and do not have a good understanding of the term or the current discourse on benefit sharing in global health research (Lairumbi, Parker, et al., 2011). Moreover, the lack of good awareness among research stakeholders, is exacerbated by the lack of comprehensive nuances on benefit sharing in international research ethics guidelines (Pratt & Loff, 2011).

Researchers have expressed the need to take benefit sharing nuances in international research seriously in order to strengthen its practice (Nicol, 2006). Taking benefit sharing seriously entails moving towards developing a substantive guide for research stakeholders on what appropriate benefit sharing should be in international research. This article is a move towards such a benefit sharing guide in international health research. The article presents categories of benefit sharing which research sponsors can consider when conducting research with participants and communities in resource poor countries. The article departs by explaining a spectrum of transactional exchange and distinguishing benefit sharing, exploitation, fair exchange and gifting. The article then presents three categories of benefit sharing in research. Based on these

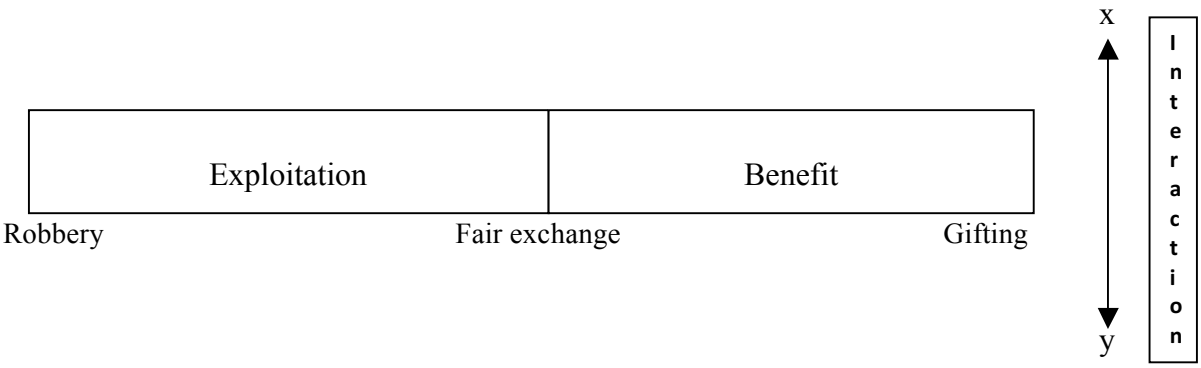
categories of benefit sharing, we provide a schematic guide of benefit sharing that would be appropriate for research sponsors involved in international research.

Benefit sharing within the spectrum of transactional exchange

Benefit sharing can be explained from a transactional exchange that can occur between two persons or groups in any given interaction. This explanation is vital in order to develop a normative justification for benefit sharing within the structure of research interaction between the research sponsors and the participants/communities. Let us consider a spectrum of transactional exchange between two parties x and y in a given interaction (Fig 1). In one end of the spectrum, the transactional exchange is in the form of *gifting* whereby party x provides goods and services to party y with no expectation of payment. An example of such transaction can be seen in charitable or humanitarian aid whereby rich countries provide goods and services to poor countries with no conditions or expectation to give anything in return. At the other end of the spectrum, the transaction is in the form of *robbery* whereby party x forcefully robs the goods and services from y without possibility of paying party y. At the middle of the spectrum, the transaction takes the form of *fair exchange* whereby both x and y equally exchange the goods and services (Fig1). Somewhere between the robbery and fair exchange in the spectrum is the possibility for *exploitation*—in which case party y has received an *unfair* payment for the goods and services they have offered even though they are not robbed. An account of exploitation cannot be complete without a reference to Wertheimer's seminal work on exploitation (Wertheimer, 1996). Wertheimer points that exploitation is a moral issue and to exploit someone is to take unfair advantage of that person. He distinguishes between *harmful* and *mutually advantageous* exploitation. Harmful exploitation would be when x takes unfair advantage of y resulting to a harmful consequence on y in the transaction. Mutually advantageous exploitation occurs when x gains excessively or unfairly in a transaction that is also beneficial to y. The counterpart to exploitation in the spectrum is a *benefit* i.e. somewhere between a fair exchange and gifting (Fig 1). A benefit is therefore an exchange whereby party y in a transaction receives goods and services that is *fairly* due their contribution in the transaction with x. Consider a hypothetical example in which two friends agreed to contribute money to start a small scale business. One of them contributes 10% of the total investment in the business while the other

puts in the remaining 90%. It is expected that the friend that contributes 10% should be given benefits or profits arising from the business that are fairly proportionate to the 10% investment. Such fair share of benefit to the friend with 10% investment cannot be said to be a gift because he/she has contributed in the business venture. It goes without saying that if the friend with the 10% investment should receive an unfair share of the benefits arising from the transaction, he/she is said to be exploited.

Fig 1: Spectrum of transactional exchange



Benefit sharing can be analyzed based on this spectrum of transactional exchange (Fig1). When a research sponsor (x) engages in a research interaction with a host community (y), it is expected that the host community should partake in a benefit sharing of goods and services arising from the research. This is because the host community has contributed (even if the contribution is little) in the research interaction with the sponsor. Moreover, because the host community has contributed to the research interaction, benefit sharing is not the same as a gifting rather an exchange that is based on contribution of the host community. With this analysis, the concept of benefit sharing can then be envisaged as a concept that has a normative justification within the spectrum of transactional exchange such that we can ascertain the rightness or wrongness of benefit sharing in a research activity. Likewise, from the analysis of exploitation, a research sponsor that excessively gains surplus benefits and provide less than the fair benefits to the community is said to exploited the community even if the research have advantages to the community (Berg, 2001). Similarly, if the sponsor provides fair benefit or even decides to give

more benefits than what the community ought to receive, the sponsor is considered to act morally right.

So what then is the right or appropriate benefit sharing that a host community ought to receive in a research interaction? The answer to this question has been inconclusive within the discourse of benefit sharing in international research. Some researchers have pointed out that the right benefits are what the community are able to negotiate with the research sponsor (Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2004). Others have argued that the right benefits are achieved if the sponsors are able to reasonably make available the products generated from the research to the host community at the completion of the research (Gbadegesin & Wendler, 2006). These approaches present advantages as well disadvantages in benefit sharing. We provide a guide to benefit sharing categories that research sponsors should consider when they conduct international research in low income countries. To present this guide, however, it is essential to refocus on the categories of benefit sharing in a research interaction.

Categories of benefit sharing in international research

In her paper King (2000) outlined three categories of benefits that are appropriate in the conduct of clinical trials. They include *direct* benefits, *collateral* or *indirect* benefits and *aspirational* benefits (King, 2000). King explains that the direct benefits arise from receiving the intervention being studied. In other words it is the benefit to direct research subjects. Collateral or indirect benefits are those that are not just for those that receive the intervention being studies but also to non study participants. For example, free laboratory or physical examination, or free medical care are all forms of indirect benefits. Aspirational benefits, as the name implies refers to the benefits arising from the study results, for future patients and to the society (King, 2000). Although, these categories are realizable in a research there are overlaps among these categories. For example, direct benefits can be confused with aspirational benefits because individual participants may think they are already benefiting from the intervention being given to them in research (King, 2000)

We can relate these categories of benefits to the concept of benefit sharing and expand it to other types of international health research asides clinical research. On this account of broadening the

categories of benefit to encompass international health research, direct benefits have essentially two features: firstly, the study intervention itself is usually the benefit and secondly, it is targeted towards the direct research participants. In order words, direct benefit sharing has a link between obtaining scientific results and achieving sustainable health gains for those enrolled in the study. For example, an experimental drug being given to participants in a clinical trial, or a new diagnostic technique that is tested on the study participants are forms of direct benefits. Some research studies whereby the community is the unit of a research intervention (e.g. community intervention studies), direct benefits is to the entire community and not the individual participants. Example, a community advocacy for a public health intervention study can be a direct benefit to the community.

Category of benefit sharing	Definition	Examples
Direct	Benefits emanating from the study intervention to direct research participants	-Access to investigational drug or intervention -Compensations for time and effort in research -Public health advocacy in a study
Indirect or collateral	Indirect gains from the study to improve health and the health care system	-Provision of basic amenities (potable water, hospitals, town halls etc) -Provision or upgrade of hospital equipments -Capacity building of staffs (on-site training, training abroad for Masters and PhD's etc)
Aspirational	Future societal benefits from the study outcomes	-Sustainable availability of public health and medical goods -Availability of proven intervention to the society

Table 1: Overview of categories of benefit sharing and some examples

The indirect or collateral benefit is distinguished from direct benefit in that it is not specifically targeted towards the study participants—rather, other identifiable individuals such as the family members of participants, or the community (King, 2000; Molyneux et al., 2012). Indirect benefits therefore, relates to indirect gains, linked to the conduct of the study, for the study

community and the health system that serves it. In other words, indirect benefit would otherwise not be available if the communities had not accepted to host a research (Molyneux et al., 2012). Example, the provision or upgrading of a hospital laboratory, training of local health staffs on a recent diagnostic technique or provision of additional health service to the local health centre (Table 1). These examples represent services that would otherwise be unavailable if the research was not conducted in the community. Aspirational benefits can be said to be a form of post-study benefit and it refers to the benefits that the future patients and the society hope to receive. The main characteristic of aspirational benefit is that it arises at the end of a study and as such it is unpredictable and dependent on whether the study generates sustainable outcomes or not. It is important to note that aspirational benefits such as post trial access should extend to all members of the society and not just access to the immediate study participants. Also, because aspirational benefit relates to the future gains from the research outcomes, the study participants are often encouraged to participate based on altruism in order to help the future generations (King, 2000).

In summary, research organizations that conduct international health research contribute to the overall global health outcomes through products that prevent and cure diseases. By developing new effective drugs and interventions, research organizations ensure that the quality of life of sick people or—what Daniels refers to as *normal species typical functioning* are restored (Daniels, 2008b). Through newly developed products such as new drugs, vaccines, diagnostic equipments, new public health interventions and generalizable knowledge that helps in understanding pathophysiological pathways of diseases—research organizations provide benefits to the research participants and in extension the community. In other words these benefits can be said to be the *fruits* of research itself. Potential fruits of research that are tested on participants during the research are considered to be direct benefits. However, because these fruits of research are subject to the successful research outcome and not immediately made available to the entire community, they are said to be aspirational benefits. All other benefits that the research communities and the health system would gain as a result of hosting the research are said to be indirect or collateral benefits.

What is the appropriate benefit sharing category in international research?

The Council for International Organization of Medical Sciences (CIOMS) refers *international research* as a sub category of clinical research where studies are conducted in Low and Middle Income Countries but externally sponsored by research organizations in high income countries (CIOMS, 2002). These organizations that externally sponsor research in Low and Middle Income Countries are either for-profit oriented (such as the pharmaceutical and biotech companies) or non-profit oriented (such as the academic institutions and charitable organizations). Research organizations should envisage providing benefits in international research within the framework of the three categories of benefit sharing. Thinking of benefits within these three categories would help in addressing the difficulty in knowing the appropriate benefit sharing research organizations should provide whenever they conduct research in resource poor countries.

As a starting point research sponsors should endeavour to provide direct benefit sharing to the research participants. In other words, because direct benefits focuses on the participants enrolled in the study, the tested intervention should contribute in making the participants better-off or at least not worse-off. Participants should be able to enjoy some benefits arising from the tested intervention during the conduct of research and should not be left with severe adverse effects. More so, individuals in resource poor countries do envisage research as opportunity to directly gain access to medical and other ancillary care. In other words, participants in resource poor countries usually consent to enrol in research because they often construe research as a means of getting better medication and ancillary care. As such, research sponsors should endeavour to provide these immediate direct benefits for the direct gains of the participants (Ballantyne, 2010).

Having delineated that direct benefit sharing should be considered in all research, what about the indirect and aspirational benefit sharing categories? should the other categories also be considered at all times in every research? Research ethics guidelines provide a strong position on the need to provide aspirational benefits to the community. For example the Council for International Organization of Medical Sciences (CIOMS) guideline indicates that any product developed in a research programme should be made available to the population involved in that research (reference to CIOMS). While we share the view that it would be morally good for

sponsors to provide aspirational benefit in research, we are of the opinion that research that there are not foreseeable future tangible benefits or those research that do not generate to any product at all should not be abandoned because participants can still benefit from the research in form of indirect benefits. We suggest that sponsors can envisage focusing on at least one of the two category of benefit sharing (indirect or aspirational) in research. To determine which of the category of benefits a research sponsor should focus on providing, there are three fundamental questions that need to be asked about the research.

Firstly, research sponsors should ask if the research they are planning to conduct research that addresses a health problem in the community or the host country. This question is vital as it underscores the importance of social value of research which delineates that research should be targeted towards the health needs of the host community (Emanuel, Wendler, Killen, & Grady, 2004). If the health research is designed to answer the health needs of the community, then the research has the potential of having aspirational benefits. In other words if research sponsors would conduct research that are tailored to the health needs of the community, then they should envisage to provide aspirational benefits. Therefore, in addition to the direct benefits which the participants would enjoy during a study, a research that is set to target the health need of the community should also envisages to provide aspirational benefits. An example is GSK Biologicals—a pharmaceutical company that is involved in malaria vaccine trials in many African countries (Agnandji et al., 2012). Conducting vaccine trials in the African communities answers the health needs of the communities as malaria is highly endemic in the continent and malaria vaccine would be highly essential in controlling malaria transmission. In the past few years, GSK had conducted vaccine trials in many African communities (Agnandji et al., 2012). These trials had provided direct benefits to the participants because those that were enrolled in the study have gained some benefits from the vaccine. The vaccine trials have shown some promising results and it is believed that when fully developed, it would be beneficial in the control of malaria in the endemic countries. As such, in addition to the direct benefits, the GSK could also think of providing the potential future aspirational benefits to the society.

For health research that is not designed to address the health needs of the host community, research sponsors should target more on providing indirect or collateral benefits to the community. For example, supposing that GSK decides to develop a drug for malaria prophylaxis instead of a vaccine, and a series of trials were conducted for the prophylactic drug in the same African region. Assuming that such prophylactic drug does not necessarily answer the health need of the host community because malaria is already endemic in Africa and prophylaxis may affect the body's natural immunity against malaria among people in the region (Doolan, Dobaño, & Baird, 2009). Prophylactic drug in this case is basically tailored to need of foreigners and tourists who travel to the malaria endemic areas. As such, for malaria prophylaxis research in African communities, research organizations should think of providing indirect benefits to the community. Indirect benefits could be insecticides treated nets, fumigation of the environments, providing laboratory services for quick testing of malaria infection, training of local health staffs on advancements in malaria control etc.

The second fundamental question is targeted at research sponsors whose research is set to answer the health need of the host community or country—i.e. those sponsors that answer on the affirmative to the first question. These research sponsors should ask if they have made adequate arrangements to ensure that the proven intervention is provided to the communities at the completion of the study. The provision of the proven intervention would entail adequate planning to ensure access to the proven intervention—on the least at an affordable price. This question is vital because research that is said to be tailored to the need of the community (the first question) does not necessarily guarantee the availability of the post-study products. Research sponsors that have made adequate arrangements to provide the proven intervention to the host community at the end of the study can be said to provide aspirational benefits to the community. Going back to the GSK example, providing aspirational benefits implies that the company has to make explicit arrangements to guarantee the provision of malaria vaccines at the end of the trial to the endemic African countries. If such arrangements are properly ensured, then GSK can resort to providing aspirational benefits in the study. So, first is to ensure that the research answers the health need of the community and secondly that there is assurance that the communities would obtain the aspirational benefits of research.

The third fundamental question is for the research sponsors that do not have adequate arrangements to provide proven intervention at the end of a study. The question is: to what extent does a research sponsor stand to gain from the outputs of the research? In other words, would the newly developed intervention generate profits for the research sponsors? This question is essential in order to distinguish between research that are for-profit oriented and the ones that are non-profit oriented. For research that are profit oriented whereby the sponsors stand to gain profits from the proven intervention, it is better for the sponsors to resort to providing indirect benefits. The indirect benefits would help in developing health capacity and infrastructures for the communities. As such research sponsors that would make profit from research products and do not have concrete arrangements to provide aspirational benefits must provide indirect benefits. For non-profit research whereby the sponsors do not stand to gain financial profits the research sponsors should liaise with host governments, international health donor organizations, and private philanthropic individuals to ensure that post-research benefits are made available to the communities.

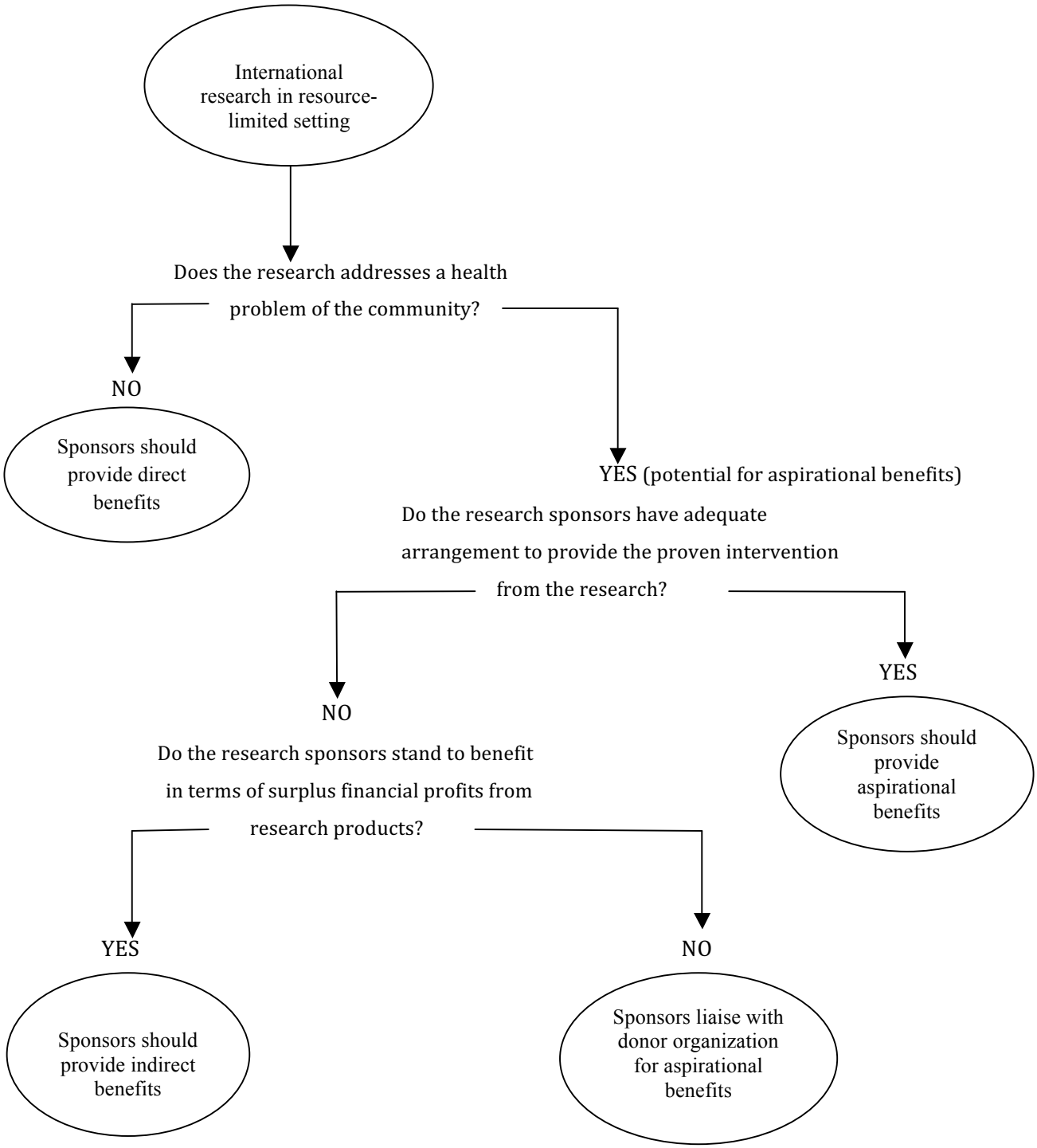


Figure 1 Three fundamental questions and the appropriate benefit sharing in research: Overview

Discussion

The guide presents an overview on the categories of benefit sharing research sponsors should provide when conducting international research in resource poor countries. While all the categories of benefit sharing are essential in the conduct of research, it is paramount to note that some categories of benefits are more vital and obligatory for the sponsors to provide. For example, it is essential that individual participants benefit directly from a tested medication in a research nonetheless; aspirational benefits whereby the society benefits from the proven medication are equally very important. For example, empirical studies have suggested that various research stakeholders prefer benefits that target more on the research host communities and country than individual participants (Lairumbi et al., 2012).

The three fundamental questions used in determining the appropriate benefit sharing categories are derived from the theoretical nuances within the concept of benefit sharing. For example, the first question on whether a research answers the health needs of a host community or country is derived from the responsiveness requirement in the conduct of research (Macklin, 2001). Responsiveness in research is iterated in the CIOMS guideline as an utmost requirement that ought to be ensured in international research. The first part of guideline 10 states that *"...the sponsors and the investigators must make every effort to ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards"*. The phrase *health needs and priorities of the host country* refer to those conditions that require urgent attention which affects people's ability to function effectively in the pursuit of fundamental life plan. As such, conducting research that address the health needs of host countries serve as a way of improving the health outcomes and reducing the research gaps in resource-limited countries (London, 2008).

Research that is said to be responsive to the health needs of a local community is not in itself beneficial unless the *fruits* of the research reach the population in the community. This affirmation underscores the relevance of the second question on whether research sponsors have adequate arrangement to make available the post study outcomes. This question is derived from the nuances of *reasonable availability* in research ethics. The second part of CIOMS guideline 10 clearly states that: "…*the sponsor and the investigators must make every effort to ensure that:*

any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community". Reasonable availability implies to make confident assertions that the proven interventions of a study will be provided to the society at the end of the study.. Proponents of reasonable availability delineate that the approach is the only way to ensure that participants and communities are not exploited in research because it offers the potential of actual benefits (Glantz, Annas, Grodin, & Mariner, 1998).

One of the major problems of reasonable availability is the emphasis on provision of aspirational benefits of research—i.e. reasonable availability focuses only on the provision of the actual study products (Gbadegesin & Wendler, 2006). An ensuing question from this problem could be: what happens if a study does not have products arising from research or if the sponsor does not have adequate arrangements to provide post-study benefits? should the research be called-off as a result of inability of sponsors to ensure aspirational benefits? The answers to these questions can be traced in the third fundamental question. The third fundamental question delineates the importance of ascertaining the commercial value of a research. Research could generate products that would lead to surplus commercial profits. Examples are seen with many multi-national pharmaceutical companies that generate drug products which subsequently generate blockbuster market profits. If such pharmaceutical companies do not have adequate arrangement to provide aspirational benefits of the research products, then it should be obligatory for them to provide indirect benefits to the host research communities. This assertion is consistent with Ballantyne's proposition on "how to conduct research in an unjust world" (2010). She noted that research sponsors that are profit driven (e.g. pharmaceutical companies and CROs) outsource trials to other countries in order to maximize profits. Because these profit driven sponsors would profit from the outcome of the research, they should—in turn provide more benefits to the already disadvantaged research communities in resource-poor settings. She called this approach the maximin (Ballantyne, 2010). The justification behinds Ballatyne's maximin is derived from Rawls account of principle of distribution as part of his Theory of Justice. He describes his maximin principle as the difference principle which requires that all social institutions be arranged to maximize the expectations of the most disadvantaged in the society (Rawls, 1999a). In other words, the lesser the favourable social conditions in a society the greater the advantages

that should accrued the society. Based on this maximin principle, Ballantyne proposes that a global research tax should be applied to commercial research sponsors conducting international health research in resource-limited countries. The global research tax should be based on the proportion of the surplus benefit generated through outsourcing of research to resource-poor settings as against conducting the same research in a developed country (Ballantyne, 2010). As such, based on the call for maximin approach, we proposed that profit oriented research organizations that do not have adequate arrangement to provide aspirational benefits must provide indirect benefits that would improve the health systems in developing countries.

Some research organizations are incapable of providing aspirational benefits due to lack of good financial stands to do that. A good example of this category is the academic institutions that do not have strong financial capital base. For such institutions it would be difficult to force them to provide benefits even if the research has generated products. For these sponsors we encourage a strong advocacy or network with affluent government and donor organization that would help in ensuring aspirational benefits. Such cooperation between academic institutions and affluent donor organization is seen in the research collaboration of some renowned universities and the Gates Foundation.

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Part Three Chapter Two: One-size- that could-fit-all: IRBs Joint Review collaboration as the key to addressing the challenges of multinational research review involving resource poor countries

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Abstract

This is a paper that sequel a main article by Barchi et al. Barchi et al highlighted the main challenges arising in the course of IRBs Ethics Review of multinational research protocols and then proposes a range of IRB collaborative mechanisms for addressing the highlighted problems. Based on these collaborative mechanisms, we developed an argument that joint IRB collaboration between the North and South is the most effective way of fostering better review process in an international collaborative research. We indicate that a joint review would provide a level playing ground where all contributions of IRBs count in the review process. Most importantly the paper also highlights that joint review process is an example of a benefit sharing process because it helps in strengthening the capacity of local IRBs in developing countries which give them confidence to conduct further reviews.

Introduction

Barchi et al highlighted the main challenges arising in the course of IRBs Ethics Review of Multinational research protocols and then propose a heuristic from a range of IRB collaborative mechanisms for addressing the highlighted problems. The range of the collaborative mechanisms are presented in a continuum starting from independent separate review to full joint review among the various IRBs involved in a multinational research. Barchi and colleagues have further demonstrated how these collaborative mechanisms address the specific challenges (Barchi, Singleton, & Merz, 2014b). We put forward that for a well efficient IRB review of international research involving resource poor countries (so-called developing countries); a joint IRB should be constituted in order to review multinational research protocols. We affirm that the joint IRB is the most vital mechanism among the collaborative mechanisms and could be all that is required for an effective multinational review

Research in resource poor settings has been shown to present unique sets of ethical and practical challenges that are distinct from the research in industrialized countries. These challenges include but are not limited to: difficulties in obtaining informed consents that are consistent with Western ethical principles, inadequate knowledge on research processes and difficulties in distinguishing between research and care delivery as well as inadequate ethics review of research protocols and weak regulatory oversights (Glickman et al., 2009). The inadequacies in ethics review in resource poor settings are mostly due to shortages of both manpower and expertise of IRBs that are responsible for research protocols review. For example an anecdotal look at the ethics committee members in Nigerian health institutions indicates that in most ethics committees there are no professional bioethicists, even though some of the ethics committee members have some form of online based research ethics trainings. In many cases research sponsors in developed countries do take advantage of the weakened ethics committee in developing countries and override the IRBs ethics review from developing countries on the grounds that such reviews are professionally deficient (Van Teijlingen & Simkhada, 2012). More so, with the high influence on research process that sponsors have over their local host communities, local IRBs risk to have little or no influence in deciding on the final outcome on ethics review even though the research is conducted in their communities. As such, due to these challenges and the inadequacies of IRB reviews in developing countries, double independent

ethical review among IRBs in multinational research involving resource poor countries may just be a mere procedural requirement due to asymmetric research influence between the North and South. This is consistent with Ravinetto's et al view that double ethical review in North-South research collaboration could be criticized as either moral imperialism because it tends to impose standards of a specific culture onto other cultures or it could be criticized as paternalistic if one considers that all countries have the capacity to enforce certain ethical standards that are unique to their population (Ravinetto et al., 2011). Similarly, Gillman et al noted that IRBs in developed countries are nearly always paternalistic and have a low regard for the quality of IRB reviews in less developed countries — even though local committees know their local populations better and are more likely to protect and care for them (Gilman & Garcia, 2004)

Therefore, independent ethical review does not necessarily depict a true review partnership or offers additional protection to research participants in developing countries research. To reflect a true IRB review partnership, we recommend that IRBs in a multinational research involving resource poor countries need to collaborate and form a single special IRB where a level playing ground for adequate research review is provided. A level playing ground for adequate review should be characterized by free deliberation, sound ethical regulation and equal interactive exchange of research expertise and cultural ideas as noted by Wahlberg et al (2013) in their suggestion on ways to cope with the problems associated with North-South international research collaboration (Wahlberg et al., 2013). This will create conditions for an atmosphere where well balanced ethical decisions that harness different ethical and cultural viewpoints are achieved. In a semi-structured interview that was meant to explore on the operations of ethics committees, a Nigerian ethics committee member stated that "our review process is usually easy because the same protocols are independently reviewed in the USA prior to our review and we hardly encounter any discrepancies because these people are the experts" This assertion gives a perception that double ethical reviews are usually one sided whereby IRBs in developed countries are the sole determinants of the review output in a multinational research. Joint review would dispel such perception among local IRBs and ensure that all IRBs in multinational research feel part of the research and that their voices count in ethical decision.

While it would require an additional effort in the research process, a joint IRB—if it is well coordinated can produce a balanced joint review committee in a multinational research. In order to set up a well coordinated joint IRB in a multinational research, the following might be an important guide in the process: Firstly, research sponsor that is to conduct a research in a particular developing country need to liaise with the national ethics governing body in that country. Many developing countries have a research ethics body at the national level that overlooks and regulate the activities as well as maintains a register of the local IRBs in various institutions across the country, for example National Health Research Ethics Committee of Nigeria, National Bioethics Committee of Uganda, National Health Research Ethics Council of South Africa etc. Secondly, the national ethics governing body—based on their knowledge of the local IRBs where the research is to be conducted can appoint member(s) of the local IRB to be part of the joint IRB in the multinational research. Moreover, there have been recorded successes in joint IRBs in multisite trials within the US, such successes can be adapted to the formulation of joint review in multinational research e.g. the Biomedical Research Alliance of New York (BRANY) IRB (McNeil, 2007). It is noteworthy to know that the joint IRB that we propose does not necessarily have to organize physical meetings where all members have to travel to a designated place. This would incur a huge logistic and financial burden on members. We are certain that with the advanced technological communication networks (teleconference etc) members can actively conduct successful meetings across the world. What counts in a joint IRB is not the physical meetings of members, but a unified fair procedure (devoid of paternalistic tendencies) where all views and expertise are adequately considered before decisions are taken.

Furthermore, joint review will strengthen the capacity of local IRBs in developing countries and give them confidence to conduct further reviews. There is a general call for research capacity strengthening in resource poor countries; so that developing countries can be empowered to be self reliant in conducting their own research. This has been shown to be a way of benefit sharing in international research (Schulz-Baldes et al., 2007). Such capacity building in health research should encompass IRBs development in resource poor countries through joint review. Also, in line with the widespread advocacy on the global justice for health and health research, the affluent countries are encouraged to see it as an obligation and help in developing health infrastructures and research capacity in developing countries (Dauda & Dierickx, 2012; Dwyer,

2005). We put forward that such global justice reasoning should inculcate joint IRB review as this will strengthen the quality of IRBs in developing countries which in turn can contribute to the development of good ethical and legal frameworks that are tailored to the peculiarities of research in developing countries.

Hitherto, we have proposed some reasons why a joint IRB review should be preferred over the independent IRB review. The question that may ensue is whether other mechanisms in the continuum as outlined by Barchi et al (open communication and the use of review consultants) (Barchi et al., 2014b) are better than joint review mechanism. It is difficult to boldly assert that other mechanisms are better or they are as effective as joint review mechanism because we do not have research evidence to indicate such claim. However Ravinetto et al expressed in their experience in conducting research in resource poor settings that open communications with other IRBs that independently review the same protocol is not effective and unnecessarily prolong time for review. Ethics committees usually do not proactively seek communications with other committee members with same ethics review task and this has resulted in inopportunity for mutual learning among the different ethics committees (Ravinetto et al., 2011). We agree that the use of review consultants—whereby review of multinational research is contracted to an independent review experts can be an effective mechanism if such consultants consist of members that have good knowledge and experiences working in developing countries(Gilman & Garcia, 2004). However, a disadvantage of the use of consultants is that members of such independent review experts are contracted and therefore are not obliged to return benefits of review expertise to the local ethics committees after the review process. As a result the local IRBs would miss the prospects for growth and development in their review engagements.

Our key point is that joint IRB review can go a long way in fostering true review partnership and curbing IRBs review challenges between North-South research collaboration. We recommend that more studies should be conducted in order to further establish the effectiveness, feasibility and other implications of joint review in multinational research involving resource poor countries.

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Summary of Major Findings

Part One: Literature review on Benefit Sharing

Part one of this doctoral project involved a literature review on the concept of benefit sharing. The literature reviews were conducted in order to understand the various nuances, discourses and arguments on the concept, not only in international health research but also in research areas involving the use of non-human genetic resources.

The **first chapter** described an evolutionary and vital trend regarding the concept of benefit sharing on the international stage. Benefit sharing was described within three major spheres or domains. Firstly, benefit sharing was described within the concept of Common Heritage of Humankind (CHH) an established international legal prescription that aims at attaining a state of equality among countries (Holmila, 2005). The major prescription of the CHH treats resources as a "common good" in which every country is entitled to share in the spoils arising from its exploration (De Jonge & Korthals, 2006). Benefit sharing, therefore is the equal sharing of benefits arising from a resource because every country has an equal stake in the resource. Secondly, benefit sharing is described within the sphere of non-human genetic resources. Within this sphere, resources can be owned by a country if such resources are found within their territorial region. Benefit sharing here is envisaged as an exchange between those who owned non-human genetic resources and those who seek to utilize these resources (Schroeder & Lasén-Díaz, 2006). The discourse of benefit sharing within the non-human genetic resources is prominent owing to the international treaty of Convention on Biological Diversity (CBD) (CBD, 1992) and its subsequent Nagoya Protocol (NP) (Nagoya Protocol, 2010). The CBD and the NP provide a strong legal instrument that aims to regulate access and benefit sharing of non-human genetic resources. The major similarity between benefit sharing in the CHH and the CBD is the fact that they are both embedded in a legally binding document. Nonetheless, the two differ in that the CHH considers resources as a "common good" belonging to countries while the CBD gives "sovereign ownership" of resources to in which countries these resources are found. Therefore, within the CBD, resources are not considered to be common goods belonging to all countries. This difference represents a significant ethical shift in benefit sharing from a concept that seeks equality among countries with respect to the sharing of resources to an instrument of exchange among countries.

Thirdly, we described the concept of benefit sharing within the sphere of international health research where it has a number of different formulations. Benefit sharing may be a form of exchange when one considers the fair benefit approach. In this case, research participants and communities can negotiate with research sponsors about the benefits they would receive upon participation in research (Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2004). Benefit sharing can also take the form of reasonable availability whereby research participants are provided with benefits of the proven intervention after completion of the study (Gbadegesin & Wendler, 2006). Likewise, benefit sharing can be envisaged as maximin in which case the research sponsors are expected to provide surplus benefits to communities because of commercial gains they would realize from the products generated following the research (Ballantyne, 2010). A notable difference between benefit sharing in international health research and the CHM and CBD is that there is no legal binding document that encompasses benefit sharing in international health research. However, we have noted that there are various ethical justifications that argued for benefit sharing are in international health research and bioprospecting research involving non-human genetic resources. Hence it was important to examine the ethical justifications of benefit sharing further.

Chapter two of this doctoral project was devoted to exploring the ethical justifications of benefit sharing. These ethical justifications are rooted primarily in the principles of justice. The systematic searches conducted in this chapter identified 33 publications that discussed various principles of justice that are given as reasons or motivations for benefit sharing in international health research and bioprospecting activities. Five components of justice were examined and their meaning within the concept of benefit sharing was analysed. These were commutative justice, distributive justice, global justice, procedural justice and compensatory justice. The principle of commutative justice was found to be highly relevant to benefit sharing, especially in the domain of research involving the use of non-human genetic resources (De Jonge, 2010; Schroeder, 2009; Vermeylen, 2007). This principle envisages benefit sharing as a tool for exchange and promotes an equivalent exchange of goods between the research sponsors and the communities. The principle of distributive justice encourages benefit sharing on the grounds of inequalities between the research sponsors on the one hand and the research participant and their communities on the other. Based on these inequalities, research sponsors should uphold benefit

sharing on the grounds of distributive justice based on the need to improve health conditions and systems in resource-limited countries (Schroeder & Pisupati, 2010; Schroeder, 2009). Global justice nuances in benefit sharing are similar to distributive justice but with a greater emphasis on a global scale considering the proliferation of globalized research. Global justice aims at strengthening benefit sharing across countries in international health research (Pratt & Loff, 2011). Procedural justice is related to benefit sharing in that the principle stresses the need to ensure all processes in achieving benefit sharing are transparent and fair (Bachmann, 2011). Therefore, the main concern of procedural justice is not on the outcome of benefit sharing but on the processes when benefit sharing outcomes are being obtained. Finally, the compensatory justice approach to benefit sharing focuses on providing participants and communities in research with compensation for their time, effort and any risks taken when participating in research (Ndebele et al., 2008).

All these principles of justice are very relevant to benefit sharing and provide a different perspective on which benefit sharing can be justified in research. These principles can also be considered to be complimentary to each other in fortifying the concept of benefit sharing. For example, distributive justice can strengthen commutative justice such that research participants and communities are entitled to benefits not just based on exchange (commutative justice) but also based on the need to develop poor health conditions in developing countries (distributive justice).

Chapter three of part one was also performed to further strengthen the justification of benefit sharing. However, we evaluated this justification of benefit sharing from the Aristotelian justice perspective. Aristotle distinguishes between two types of justice namely universal and particular justice. The universal justice pertains to actions that are in accordance with the law such that a person acting in accordance with universal justice is said to act in accordance with the law governing a certain action (Aristotle, 2011). Therefore in Aristotelian universal justice, benefit sharing would denote acting in accordance with the law governing benefit sharing. Therefore, research organizations would be considered to be acting in a good way if they abide by the law governing benefit sharing e.g. the Nagoya Protocol on Access and Benefit Sharing. Nonetheless, acting in accordance with the law on benefit sharing is not sufficient as benefit sharing in

international health research involving human subjects is not covered by any legal framework (CBD COP Decision II, 1995). The regulations on benefit sharing in human subjects research are presented in the form of non-binding ethics regulations. Therefore, a benefit sharing justification must be established outside the box of legal underpinning. This justification is outlined in the Aristotelian particular justice (Aristotle, 2011). This justice perspective is based on the ethical underpinnings of distributive justice, commutative justice and restorative justice which we have already established to be relevant in the nuances of benefit sharing.

Part Two: Empirical Research on the Concept of Benefit Sharing

The research work reported in part two tests some of the salient findings that emerged in part one. The work utilized an empirical method of inquiry with stakeholders involved in international health research. In this section we raised the issues identified within the literature review that remain inconclusive within the discourse of benefit sharing. We noted in the first chapter of part one that there is controversy associated with what the concept of benefit sharing entails and what might be an appropriate definition. We incorporated this important assertion in the empirical studies in order to obtain the perspectives of the respondents. Another area of the literature review that informed the empirical research part two pertains to justifications for benefit sharing. The main focus of the second and third chapters of part one was aspects of justice associated with benefit sharing. These nuances of justice in relation to benefit sharing were therefore raised in the empirical study in order to assess if there are other justifications on which benefit sharing should be built. Furthermore, the important aspect of legal frameworks of benefit sharing that was discussed in chapter one, part one, has also been carried forward to part two. We assess the views of the respondents in the empirical research on their thoughts on developing a legal framework of benefit sharing in international health. This empirical work is divided into two parts.

The **first chapter of part two** reports the results of 10 semi-structured interviews conducted with stakeholders from Research Ethics Committees in Nigeria. The aim was to provide the perspective of the stakeholders on the concept of benefit sharing. The stakeholders were selected from the list of eligible Research Ethics Committees made available by the National Health Research Ethics Committee—a national body that controls the affairs of all ethics committees in

Nigeria. The stakeholders were asked questions pertaining to various aspects of benefit sharing and also their general experiences of the review process of international research protocols. Stakeholders expressed different degrees of understanding on the concept of benefit sharing in international research. These differences in understanding were thought to be attributed to the lack of a succinct definition on the concept of benefit sharing in international health research. Furthermore, the research results suggested that benefit sharing is not a well known concept among the stakeholders compared to a concept like informed consent. Nonetheless, participants agreed that benefit sharing is a good ethical concept that should be upheld in research ethics. Also with regard to the processes required to achieve benefit sharing, stakeholders delineated three ways in which good benefit sharing can be achieved: (1) negotiating between the research sponsors and the community representatives, (2) allowing the ethics committees to decide on the benefits that are best suited to the research participants and the communities, and (3) letting research sponsors decide on the benefits they wish to provide to the research participants and communities. With regard to justifications of benefit sharing, stakeholders shared varying opinions on whether benefit sharing in international research should be put into a legal binding framework in order to strengthen its justifications. In general, stakeholders that favoured the development of a legal framework believed that such a framework would help in checking corrupt practices in research, especially in corruption prone countries such as Nigeria. Also, a benefit sharing law would ensure that at all times benefits are accrued to the participants and communities. The stakeholders that were against a benefit sharing law expressed the view that a law would place a burden on research sponsors and subsequently discourage research conduct in developing countries. Likewise, they felt that a benefit sharing law would create a situation whereby participants hastily think of benefits without good assessment of the risks associated with research. On the issue of which benefits are appropriate for research participants and communities, the respondents expressed that research benefits can be direct to research participants such as the intervention tested in research and incidental findings during research. Alternatively, it may be in form of something that is of benefit to the whole community e.g. provision of hospital equipment. Although respondents expressed that benefits to the participants and communities could take any form, many preferred benefits that target the entire community rather than those that are specific to the individual research participants.

The **second chapter of part two** presents a similar empirical research study as reported in the first chapter. The main difference is the target research stakeholders. Unlike the research respondents in the first study, chapter two recruited stakeholders working in European research organizations that are significantly involved in international health research in Low and Middle Income Countries. A total of 11 semi-structured interviews were conducted with stakeholders from Europe working in pharmaceutical companies, academic research institutions and non-governmental organizations. The respondents asked about the various aspects of benefit sharing and their experiences in research engagements in developing countries. The results showed some similarities relating to respondents understanding on benefit sharing. These respondents also expressed different viewpoints on what they understand by the concept of benefit sharing. Benefit sharing was viewed as a partnering with local health staff during research, capacity building of research participants and local research staff, and exchange of goods and services in research activities. Although the respondents expressed different views on benefit sharing, their responses indicated that they are conversant with its nuances. Respondents highlighted that benefit sharing practices in their organizations are mostly motivated by elements of justice and based on organizations' Corporate Social Responsibility (CSR). They also noted that, in their opinion, benefit sharing should not only focus on research in developing countries but should intersect all research studies, irrespective of the context. With regard to the legal framework on benefit sharing, the respondents voiced similar views as the first empirical study. They felt that a legal framework would be difficult to implement. They noted that deciding what to include in the law would be a major issue in addition to the concerns expressed in the first study which identfied that a legal framework would discourage research conduct in developing countries.

Part Three: Normative Ethical Reflection on Benefit Sharing

Part three of the doctoral research project was motivated by parts one and two. This part consisted of two sections which were aimed at a critical ethical reflection on the ways to improve benefit sharing practices. In the literature review and the empirical studies we have shown that benefit sharing has no consistent or succinct meaning in international health research. For example, in the empirical research, respondents were shown to have different understandings of benefit sharing. Although we do not think that these different meanings presented by the

respondents are problematic, we believe that the concept of benefit sharing needs to be bolstered through a normative analysis within a spectrum of transactional exchange. In other words, the lack of consistent definition of benefit sharing has highlighted the need to provide a normative framework for benefit sharing and prompted us to offer some recommendations on the practice of benefit sharing in international health research in part three, chapter one. Part three, chapter two shifts its focus from benefit sharing nuances to practical recommendations in favour of a joint ethics review between North and South IRBs. This shift reflects the initial intension of the paper which was aimed at providing a different perspective from a published article on fostering IRB collaboration for international research. However, this chapter is incorporated as part of the thesis because of its unique and practical recommendations on a very important aspect of benefit sharing, capacity building. I outline chapters one and two of part three of this doctoral thesis in more detail below.

Chapter one of part three begins with an evaluation of benefit sharing within a spectrum of transactional exchange. This analysis was important in order to provide benefit sharing with a normative value in human interactions, such as in research interactions between the research sponsors and participants/communities. A normative value of an action gives it an ethical underpinning to determine the "rightness" or "wrongness" of the action. As such, the normative evaluation of benefit sharing was performed in order to set benefit sharing as a prescriptive concept that can be judged to be either morally right or wrong. We then outlined a general categorization of benefits that are often described in research ethics literature and publications. These categories of benefits were: direct benefits, indirect or collateral benefits and aspirational benefits. We argued that viewing benefit sharing through these categories is not all-encompassing and can result to some unresolved issues in benefit sharing formulation. We then offer a benefit sharing recommendation that is dependent on three fundamental questions in research. These questions are relevant in setting the appropriate benefits to be provided to the participants and communities for their engagement with the research sponsors.

Chapter two is a reflection on a capacity building activity for ethics committees in developing countries that are involved in the review process of international collaborative research. Capacity building for ethics committees in developing countries is an integral part of benefit sharing. This

is because improving the capacity of local staff subsequently leads to improvement in the health service delivery, which is a benefit to the community. We argued that to foster a better research collaboration, it is essential to promote a joint review process between the South and North ethics committees as opposed to independent review process whereby research protocols are submitted to the North and South ethics committees separately in a collaborative research project. We noted that independent review does not reflect a true collaboration. Moreover, ethics committees in the South do not have adequate capacity for review of protocols compared to the committee in the North. This inadequacy can result in paternalistic practices whereby the ethics committees in the North can overrule and even disregard review outcomes of committees in the South. We therefore argued that a joint ethics review is the solution to the current challenges faced by independent review processes between North and South collaborative research. A joint ethics review process would not only strengthen capacity but also ensure true partnership between North and South ethics committees in an international collaborative research project. A joint review process creates a level playing ground for adequate review which is characterized by free deliberation, sound ethical regulation and equal interactive exchange of research expertise and cultural ideas. We outlined procedures that are vital in order to form a successful joint ethics review between the North and South. These include a good liaison between research sponsors and the national ethics regulatory body in the host country, national ethics regulatory body assessment, and appointment of local ethics committees to be part of the joint review process. Implementation of these processes would develop a stronger collaboration and strengthen capacity and boost confidence of the local ethics committees.

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General Conclusion and Recommendations

This thesis provides insights on the concept of benefit sharing in international health research through a review of the literature that presented a general overview on what benefit sharing entails. We looked at the historical development of the concept of benefit sharing in the Common Heritage of Humankind, Convention on Biological Diversity and International Health Research. Specific views of principles of justice, as well as Aristotelian justice in relation to benefit sharing, were also investigated. This was helpful in establishing the relevance of justice principles as important concepts in the justification of benefit sharing. We established despite the fact that benefit sharing has no legal framework within international health research, the concept has gained ethical justifications rooted in the principles of justice. Our empirical research has shown that the concept of benefit sharing is widely accepted among research stakeholders as a "good" ethical concept, although it is a concept that still requires more publicity in the domain of research ethics. This is evidenced by our finding that Ethics Review Committees in Nigeria can recognize ethical concepts such as informed consent more easily compared to benefit sharing. Although, they have a good understanding of what benefit sharing entails in research and may even have good benefit sharing requirements in practice, we still hold the view that there is a need for more advocacy in order to increase the awareness on benefit sharing among international health research stakeholders. We recommend more research specifically on methods that will foster the advocacy of benefit sharing in international health research. Similarly, more research is required to determine the relationship between corporate social responsibility and benefit sharing. This is important because of the growing emphasis of many multinational companies on the relevance of corporate social responsibility.

Based on the literature review and the empirical studies, we have identified that there is no succinct definition of benefit sharing that fits international health research. Respondents in the empirical research have various understandings about benefit sharing including as financial payment to participants, treatment of participants for any adverse effects, and capacity building for research. However, we have proposed a broad definition of benefit sharing that fits international health research. Benefit sharing represents an aggregate of all the gains and advantages that should accrue to the research participants and communities in international health research in order to improve the social value of research and to ensure justice. We established justice as the main motivation to give back to the society where research is

conducted. We also highlighted that corporate social responsibility is mentioned as a reason for benefit sharing. From the empirical studies, it can be depicted that there is no one-size-fits-all concept of benefit sharing in international health research. However, we have developed a normative basis for benefit sharing within a transactional spectrum of interaction and put forward a recommendation that will be helpful in deciding the right benefit sharing in an international health research. It is important to mention that our recommendation in part three, chapter one of the thesis relies more on transaction specific research—i.e. when there is a specific research interaction between the research sponsors and the research participants/communities. However a broader look at benefit sharing that focuses on a macro level of social justice rather transaction specific should be encouraged(Benatar & Singer, 2010; Ijsselmuiden, Kass, Sewankambo, & Lavery, 2010; Lavery et al., 2010). This approach looks beyond a specific research transaction and takes into account the background injustices of the context in which the transaction occurs. In commending a broader look at benefit sharing as compared to transaction specific approach, London argues that a "*transactional approach to fairness serves to "screen out" precisely the kind of information that makes concerns about justice in Low and Middle Income Countries relevant, namely the extent to which populations and host country communities may have arrived at their circumstances of poverty and deprivation through unjust treatment by their own authorities, and/or international institutions and relationships that are unfair and oppressive*" (London, 2005).

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Academic activities during the PhD

The journey of my doctoral research project started in October, 2011 shortly after the completion of the Erasmus Mundus Master of Bioethics program. I started with a general reading of the

literature on the ethical aspects of research in developing countries. This was necessary in order to acquaint myself with the current trends in research ethics in developing countries. This was also essential in order to set the tone for the design of the doctoral project plan.

The doctoral plan was designed in conjunction with the project promoter Professor Dierickx who also guided and contributed in each step of the plan execution. The first stage was basically a literature review and was conducted in order to obtain a general knowledge and to familiarize myself on the topic of benefit sharing. The literature review was also needed to delineate the emerging concepts, ideas and burning issues surrounding the topic of benefit sharing. The exercise of literature review sets the ground for the second part of the doctoral plan which is the empirical studies. During the empirical study I gained a travel scholarship from the KU Leuven in order to conduct research in Nigeria and a short research stay at the Kaduna State University, Nigeria. During my two month stay in Nigeria, I conducted research with Ethics Committees who are responsible for the institutional review of research protocols. I was given an office space at the Kaduna State University where I organized my research work and arranged for each interview to be conducted. My plan to deliver a lecture for the medical students of the University was thwarted by strike activity which brought to a halt all academic activities. However, I developed an abstract with the staff of the Centre of Medical Law and Ethics of the University which was subsequently accepted for oral presentation at the UNESCO Bioethics Conference in Naples, Italy.

On my return from Nigeria, I set out for the second part of the empirical study which involved interviews with research stakeholders in Europe that are involved in the conduct of research in Low and Middle Income Countries. These interviews were conducted concurrently with the analysis of the interviews from Nigeria.

Besides these activities connected to the research project, I also performed other academic activities within and outside the KU Leuven environment. During the first year of the doctoral project, I presented my preliminary doctoral plan where I explained the plan activities for the research work to a panel of jury members and colleagues. During the course of the year I attended conferences and seminars and given poster and oral presentations. Some of the notable conferences include the Conference on the Added Value of One Health in Copenhagen, Denmark

and the European Association of Centres of Medical Ethics Conference in Lille, France and a Symposium on the Health System Research in Developing countries in Geneve, Switzerland.

Furthermore, as a scholar working on the ethical aspect of research in developing countries, I have organized a one day departmental seminar on Research Capacity Building and Benefit Sharing in Low and Middle Income Countries. The seminar invited two external speakers and members to deliberate on the topic. In the same vein, I have delivered lectures to Master of Biomedical Science students of KU Leuven on Ethical Issue in Research in Developing Countries. This was relevant for them to have a perspective of challenges on the conduct of research in developing countries